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The American Journal of Medicine

Vol. XXIX OCTOBER 1960 No. 4

CONTENTS

Editorial

- A View of Gout as Inborn Error of Metabolism ALEXANDER B. GUTMAN 545

Clinical Studies

- The Renal Excretion of Hydrogen Ion in Renal Tubular Acidosis. I. Quantitative Assessment of the Response to Ammonium Chloride as an Acid Load
J. R. ELKINTON, E. J. HUTH, G. D. WEBSTER, JR. AND R. A. McCANCE 554
- The Renal Excretion of Hydrogen Ion in Renal Tubular Acidosis. II. Quantitative Response to the Carbonic Anhydrase Inhibitor, Acetazolamide
G. D. WEBSTER, JR., E. J. HUTH, J. R. ELKINTON AND R. A. McCANCE 576
- The Renal Excretion of Hydrogen Ion in Renal Tubular Acidosis. III. An Attempt to Detect Latent Cases in a Family; Comments on Nosology, Genetics and Etiology of the Primary Disease E. J. HUTH, G. D. WEBSTER, JR. AND J. R. ELKINTON 586
- The first paper of this detailed study of renal tubular acidosis deals with a method for quantifying the renal excretion of hydrogen ion by means of a standardized ammonium chloride loading test. The results of the test are ingeniously expressed as a hydrogen ion "clearance" index. Armed with this method, the authors examined five adult patients with renal tubular acidosis and found that all had a lower than normal "clearance" index, due primarily to impaired ability to excrete hydrogen ion as titratable acid, but for varied reasons. It is concluded that renal tubular acidosis may involve disturbances in more than one mechanism of acid excretion. The second paper explores the possibility, by use of acetazolamide, that carbonic anhydrase deficiency of the renal tubular cells may be one of the causes of renal tubular acidosis; the results were equivocal. The third paper describes the occurrence of overt and latent renal tubular acidosis (the latent cases disclosed by the hydrogen ion "clearance" test) in several adult as well as juvenile members of a family, suggesting a genetic factor. Analysis of the literature reveals two apparently distinct forms of primary renal tubular acidosis: one, infantile, appears in the first year of life, has a high rate of recovery, and is a predominantly male disorder. The other occurs later in life, has a low cure rate (although responding as long as appropriate therapy is given) and involves females for the most part.
- Idiopathic Paroxysmal Myoglobinuria. Report of Two Cases Occurring in Sisters. Review of the Literature . . . MUNSEY S. WHEBY AND HENRY S. MILLER, JR. 599
- An informative account of this disorder, with two cases in sisters, the only ones known to be involved in a family of six siblings.

Contents continued on page 5

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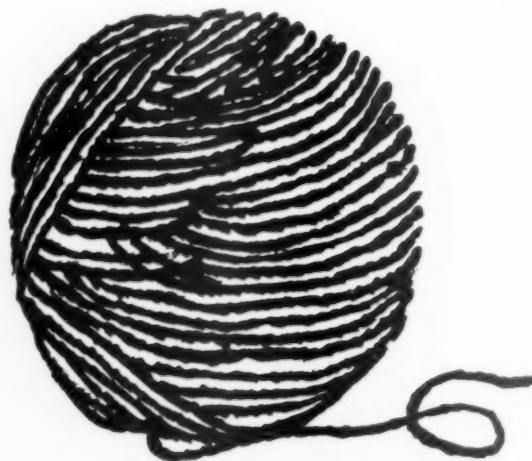
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*Duncan, G. G.: Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment, ed. 4, Philadelphia, Saunders, 1959, p. 795.

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CONTENTS continued—October 1960

VOLUME TWENTY-NINE

NUMBER FOUR

The Renal Concentrating Defect in Sickle Cell Disease

MARVIN F. LEVITT, A. DANIEL HAUSER, MARSHALL S. LEVY
AND DEMETRA POLIMEROS 611

It has long been appreciated that sickle cell anemia is associated with a defective capacity of the kidney to concentrate urine but the site and nature of this defect have not been clarified. The phenomenon is documented and studied in this communication, and an ingenious explanation, based on current concepts of the normal concentrating mechanism, is offered. The authors suggest that the difficulty in sickle cell disease lies in the ineffective trapping of solute in the medullary circulation of the kidney, and speculate as to the anatomical basis for this abnormality.

The Lungs in Rheumatoid Spondylitis. Gas Exchange and Lung Mechanics in a Form of Restrictive Pulmonary Disease

DAVID M. TRAVIS, CHARLES D. COOK, DESMOND G. JULIAN, CHARLES H. CRUMP,
PER HELLIESEN, EUGENE D. ROBIN, THEODORE B. BAYLES
AND C. SIDNEY BURWELL 623

Because of impaired rib motion and fixation of the spine, patients with rheumatoid spondylitis have restrictive alterations in pulmonary function, as demonstrated in this study of sixteen patients. Ventilation-perfusion relationships, intrapulmonary gas mixing and airway resistance were all unaffected. No alveolar hypoventilation was noted.

The Spatial Vectorcardiogram in Left Bundle Branch Block and Myocardial Infarction, with Autopsy Studies . . . N. DEPASQUALE AND G. E. BURCH 633

The electrocardiographic diagnosis of myocardial infarction in the presence of left bundle branch block has generally been held, since Wilson's time, to be impossible, although various schemes for accomplishing this have been proposed. The present study supports the view that patients with left bundle branch block and myocardial infarction show distortions in the QRS sE-loop not found when left bundle branch block is unaccompanied by myocardial infarction, thus facilitating the diagnosis under conditions in which the conventional electrocardiographic leads alone could not do so.

Hemodynamics During Induced Cardiac Tamponade in Man

JOHN T. SHARP, IVAN L. BUNNELL, JAMES F. HOLLAND, GERAINT T. GRIFFITH
AND DAVID G. GREENE 640

The decreased inspiratory stroke volume and enhanced respiratory effect on the pulse characteristic of cardiac tamponade was found in man (as in the dog) to be due to diminished effective ventricular filling gradient. The hemodynamic implications are discussed informatively, as are the current misconceptions of the meaning of the term "paradoxical pulse" which, as the authors make clear, has long outlived its usefulness.

Contents continued on page 7

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CONTENTS continued—October 1960

VOLUME TWENTY-NINE

NUMBER FOUR

Asterixis in Non-Hepatic Disorders HAROLD O. CONN 647

Asterixis, the flapping tremor seen in hepatic coma, was observed in twelve patients without primary liver disease. It appears to be a non-specific neurological finding which may accompany organic delirium in a variety of metabolic and toxic disorders which interfere with cerebral metabolism. Possible factors such as hypoxemia, or derangements in serum electrolytes, carbon dioxide content, blood ammonia concentration or pH were evaluated, but none was found consistently.

The FII Agglutinating Factors in Serums of Patients with Non-Rheumatic Diseases DAVID S. HOWELL, JANET M. MALCOLM AND ROBERT PIKE, WITH THE TECHNICAL ASSISTANCE OF BETTY BROOME 662

It is becoming increasingly apparent that the various serologic tests for rheumatoid arthritis, while usefully specific, give positive reactions in a significant proportion of patients with certain other diseases. This applies, for example, to hepatic disorders, and the present investigation is concerned with a study of the serum protein components in liver disease which have properties similar to those of the rheumatoid agglutinating factor. It develops that these too are 19S macroglobulins, indistinguishable in the characteristics examined from those occurring in rheumatoid arthritis.

Reviews

Pulmonary Mechanics. A Unified Analysis of the Relationship Between Pressure, Volume and Gasflow in the Lungs of Normal and Diseased Human Subjects DONALD L. FRY AND ROBERT E. HYATT 672

The authors have devised an ingenious three-dimensional graphic representation of the mechanics of pulmonary ventilation, relating transpulmonary pressure, respiratory flow and lung inflation. Analysis of the three-dimensional surface, derived from isovolume pressure-flow curves, has a conceptual value and is applied by the authors to the normal and abnormal lung. The study offers another approach to elucidation of the mechanics of breathing in disease states.

Acromegaly . . . GEORGE J. HAMWI, THOMAS G. SKILLMAN AND KENNETH C. TUFTS, JR. 690

An instructive analysis of the clinical and laboratory findings in twenty-seven patients with progressive acromegaly, before and after treatment, and three patients with inactive acromegaly. Most of the data are in agreement with previous reports. Of special interest, because of the paucity of prior reports, are the results of treatment by radiation and/or surgery.

Clinicopathologic Conference

Friedländer Pneumonia, Hypocalcemia and Renal Failure 700

Clinicopathologic Conference (Washington University School of Medicine)

Contents continued on page 9

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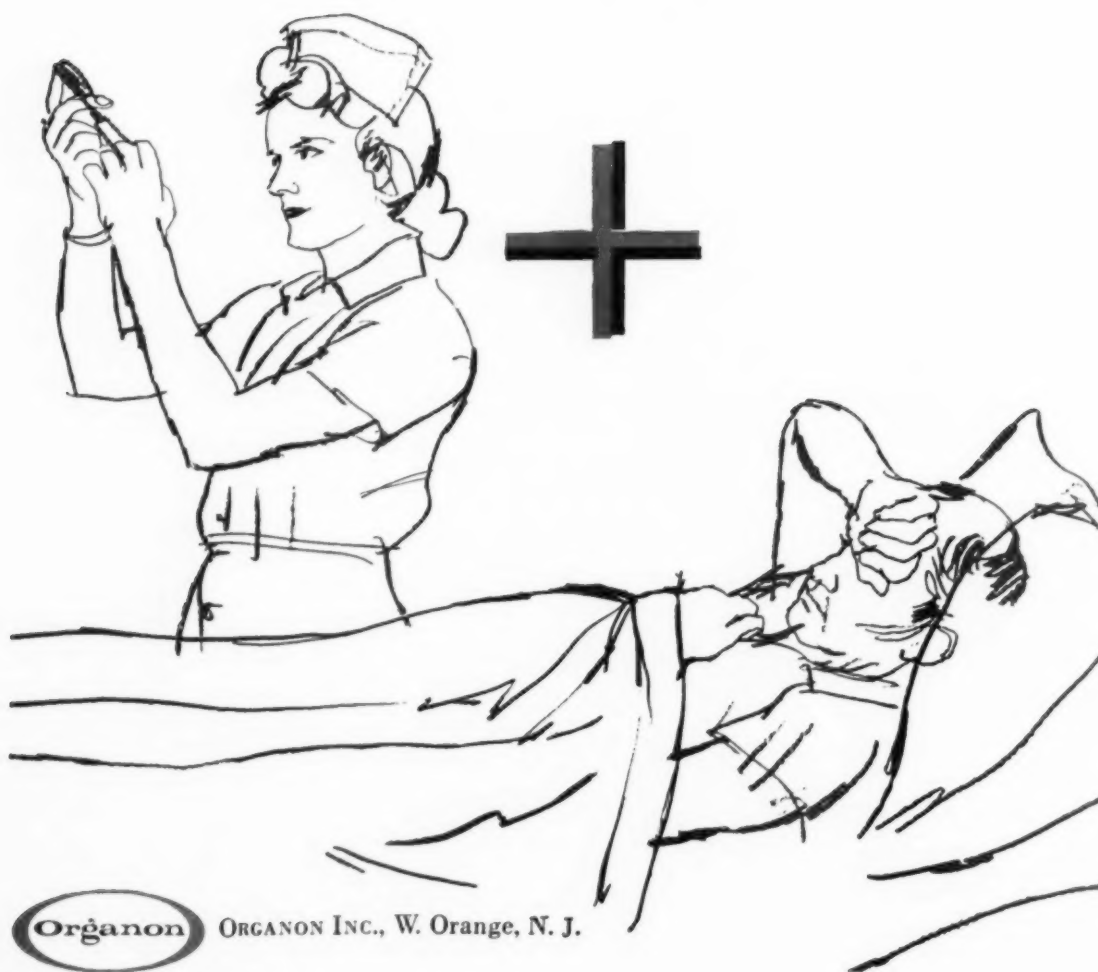
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CONTENTS continued—October 1960

VOLUME TWENTY-NINE

NUMBER FOUR

Case Report

Pulmonary Alveolar Proteinosis with Unusual Complicating Infections. A Report of
Two Cases. CARROLL C. JONES 713

Two interesting examples of this obscure disorder are described.

The November issue will contain a

Symposium on Peptic Ulcer

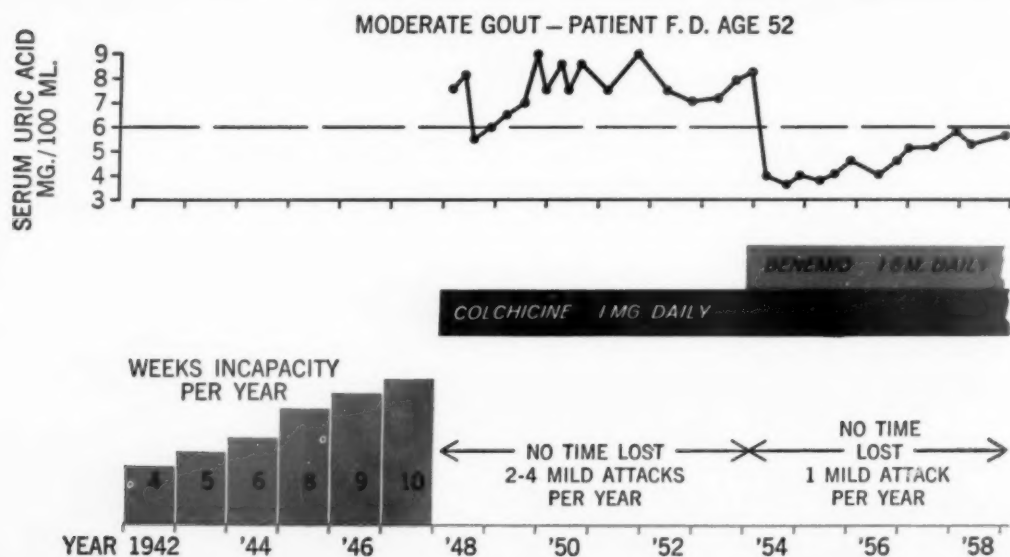
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Advertising Index on Pages 157 and 158

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1. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, pp. 162, 163. 2. Talbott, J. H.: Gouty arthritis, Minn. Med. 42:1044, Aug. 1959. 3. Talbott, J. H.: Recognition and treatment of gouty arthritis, Current Medical Digest 26:57, Nov. 1959.

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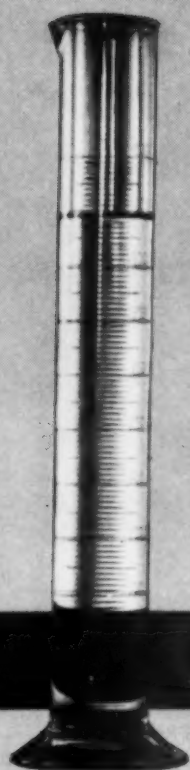
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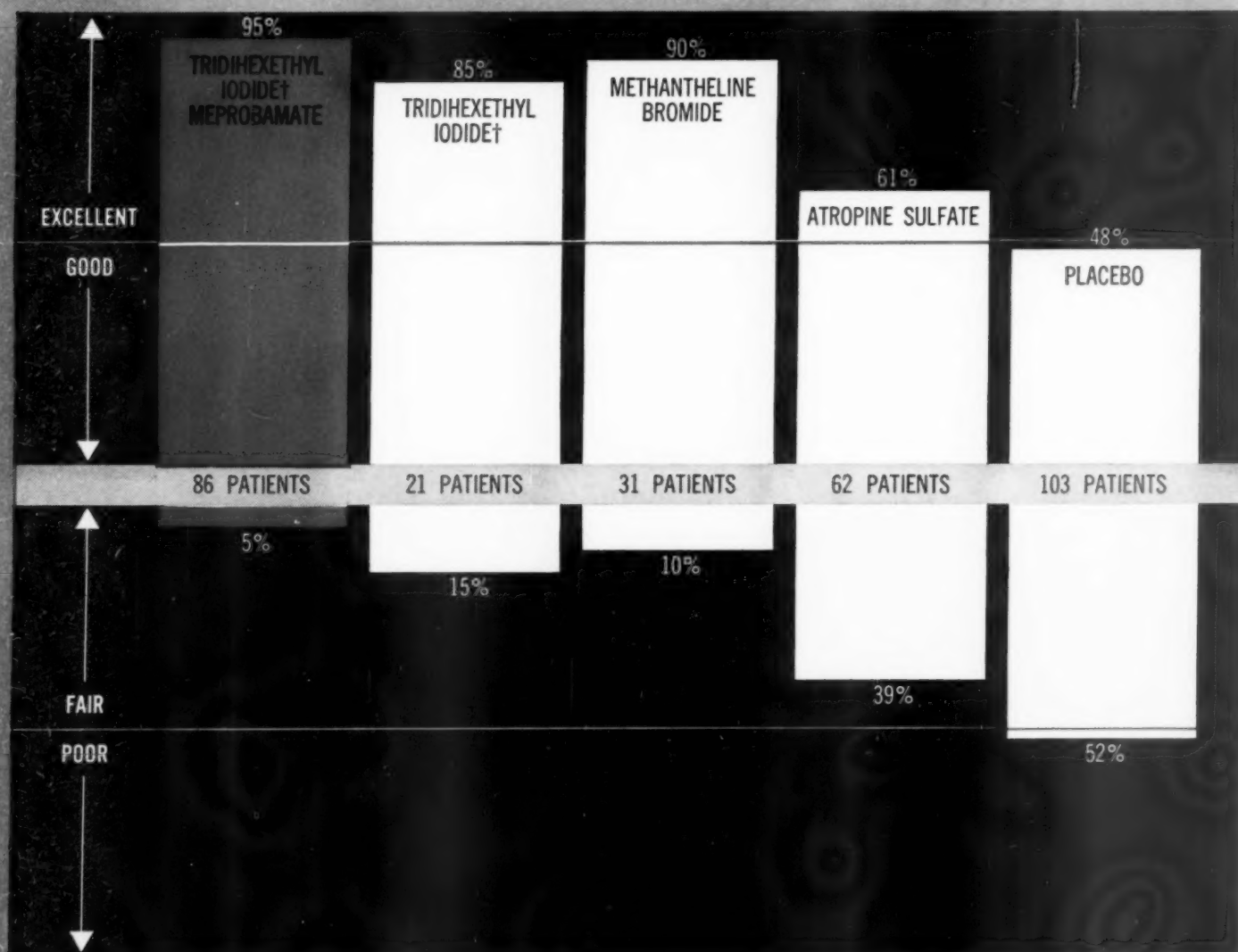
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Consult literature and dosage information, available on request, before prescribing.

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clinically proven efficacy..

in relieving tension... curbing hypermotility and excessive secretion in G.I. disorders



PATHIBAMATE combines two highly effective and well-tolerated therapeutic agents:

Meprobamate—widely accepted tranquilizer and

PATHILON tridihexethyl chloride—anticholinergic noted for its effect on motility and gastrointestinal secretion with few unwanted side effects.

Contraindications: glaucoma, pyloric obstruction, and obstruction of the urinary bladder neck.

Two available dosage strengths permit adjusting therapy to the G.I. disorder and degree of associated tension.

Where a minimal meprobamate effect is preferred...

PATHIBAMATE-200 Tablets: 200 mg. of meprobamate; 25 mg. of PATHILON

Where a full meprobamate effect is preferred...

PATHIBAMATE-400 Tablets: 400 mg. of meprobamate; 25 mg. of PATHILON

Dosage: Average oral adult dose is 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

Pathibamate[®] 400 200

meprobamate with PATHILON[®] tridihexethyl chloride Lederle

clinically proven safety

The efficacy of **PATHIBAMATE** has been confirmed clinically in duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, and gastric hypermotility.

Pictured are the results obtained with the **PATHILON** (tridihexethyl iodide)—meprobamate combination† in a double-blind study of 303 ulcer patients, extending over a period of 36 months.* They clearly demonstrate the efficacy of **PATHIBAMATE** in controlling the symptoms.

SIDE EFFECTS	TRIDIHEXETHYL IODIDE† MEPROBAMATE	TRIDIHEXETHYL IODIDE†	METHANTHELINE BROMIDE	ATROPINE SULFATE	PLACEBO
DRY MOUTH	1%	5%	72%	46%	5%
STOMATITIS	1%	0%	28%	14%	0%
VISUAL DISTURBANCES	0%	0%	50%	34%	1%
URINARY RETENTION	0%	0%	18%	11%	1%
DROWSINESS	20%	0%	0%	0%	0%
COMPLICATIONS OR SURGERY					
HEMORRHAGE	0%	9%	3%	9%	10%
PERFORATION	0%	0%	0%	6%	0%
OPERATION	0%	5%	5%	14%	2%
RECURRENCES					
NONE	28%	23%	25%	17%	26%
FEWER AND Milder	67%	62%	52%	37%	24%
SAME OR MORE	5%	15%	23%	46%	50%

*Atwater, J. S., and Carson, J. M.: Therapeutic Principles in Management of Peptic Ulcer. *Am. J. Digest. Dis.* 4:1055 (Dec.) 1959.

†PATHILON is now supplied as tridihexethyl chloride instead of the iodide, an advantage permitting wider use, since the latter could distort the results of certain thyroid function tests.



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

control the tension — treat the trauma

inner
protection



Tain

(Triacetyloleandomycin, Triaminic® and Calurin®)

to
contain
the
bacteria-prone
cold

safe antibiotics

Triacetyloleandomycin, equivalent to oleandomycin 125 mg. This is the URI antibiotic, clinically effective against certain antibiotic-resistant organisms.

fast decongestion

Triaminic®, 25 mg., three active components stop running noses. Relief starts in minutes, lasts for hours.

well-tolerated analgesia

Calurin®, calcium acetylsalicylate carbamide equivalent to aspirin 300 mg. This is the freely-soluble calcium aspirin that minimizes local irritation, chemical erosion, gastric damage. High, fast blood levels.

TAIN brings quick, symptomatic relief of the common cold (malaise, headache, muscular cramps, aches and pains) especially when susceptible organisms are likely to cause secondary infection. Usual adult dose is 2 Inlay-Tabs, q.i.d. In bottles of 50. R only. Remember, to contain the bacteria-prone cold...TAIN.

SMITH-DORSEY • LINCOLN, NEBRASKA

a division of The Wander Company

(+)= DESBUTAL GRADUMET



New Desbutal® Gradumet® brings together two classic drugs

in an ingenious, long-acting vehicle that "meters"
its release as surely as the ticking of a clock

Predictable . . . uniform . . . and of daylong duration. This is the drug release pattern Abbott now offers in the new Desbutal Gradumet form.

The component drugs (Desoxyn® and Nembutal®) have a distinct, coordinated release pattern. Because they act at different sites of the brain, the mood is elevated and the patient is calmed.

The remarkable thing is that the Gradumet release timing is totally independent of digestive activity. Minute by minute throughout the day, the patient is receiving medication. In the pages that follow, you'll see some of

the Gradumet features dramatized. Just remember: When writing, specify Desbutal Gradumet.

Indicated for anorectic effect in obesity; also for counteracting depression associated with anxiety, and tension in psychosomatic disorders, neuroses, mild psychoses and other conditions. Usual all-day dosage is one Desbutal Gradumet. In two strengths, Desbutal 10 Gradumet (10 mg. of Desoxyn and 60 mg. of Nembutal) and Desbutal 15 Gradumet (15 mg. of Desoxyn and 90 mg. of Nembutal).



®DESXYN—METHAMPHETAMINE HYDROCHLORIDE, ABBOTT.

®NEMBUTAL—PENTOBARBITAL, ABBOTT.

®GRADUMET—LONG-RELEASE DOSE FORM, ABBOTT; PAT. APPLIED FOR.

010-285

on-the-go relief from recurrent throbbing headaches

including migraine
syndromes,
other vascular
headaches,
histaminic
cephalalgia,
and occipital
neuralgia

Medihaler-[®] Ergotamine

Oral Inhalation of
Micronized Ergotamine Tartrate

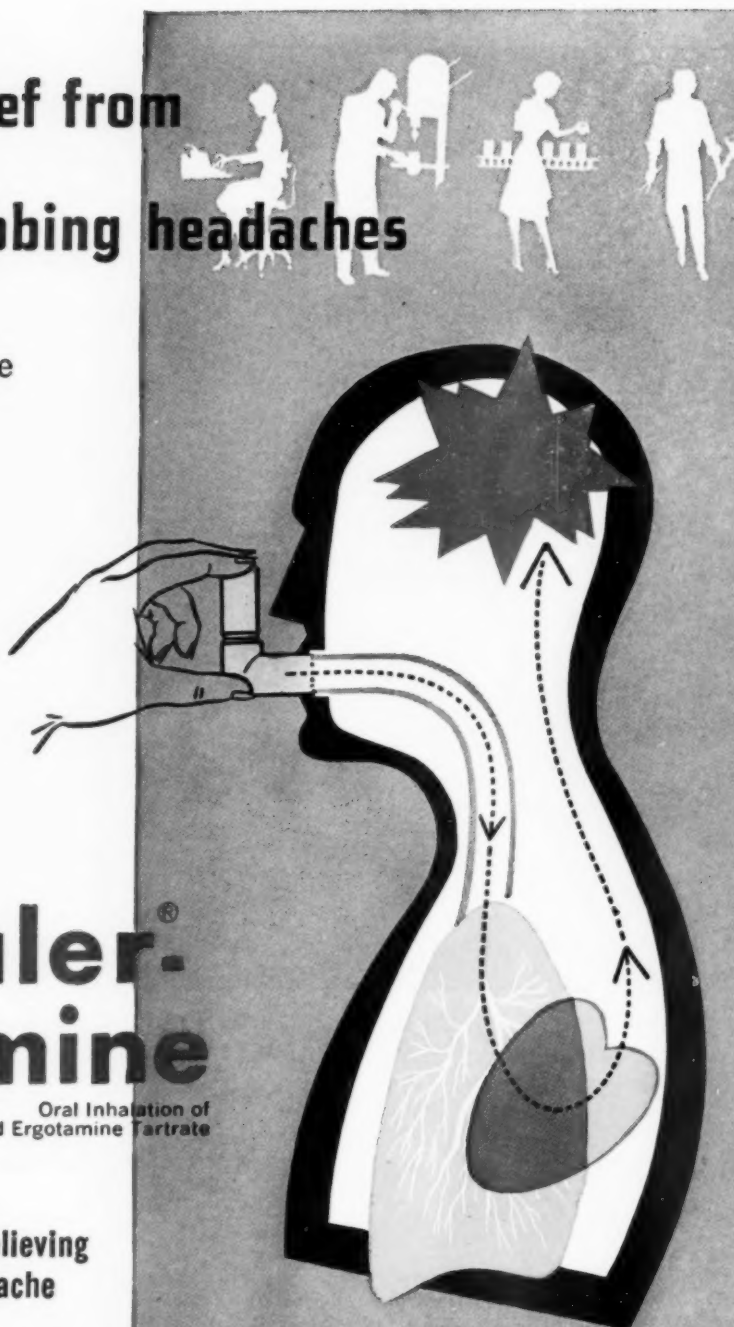
**Fastest overall method for relieving
recurrent throbbing headache**

Approximates speed and predictability of relief following ergotamine injection.

Eliminates delay in treatment...Medihaler travels *with* the patient...ready and in use in 5 seconds!

"In a series of over 300 episodes of vascular headache in 41 patients 'Medihaler'-Ergotamine was effective in about 70%."

Graham, J.R.: Faulkner Hospital,
Jamaica Plains, Boston.



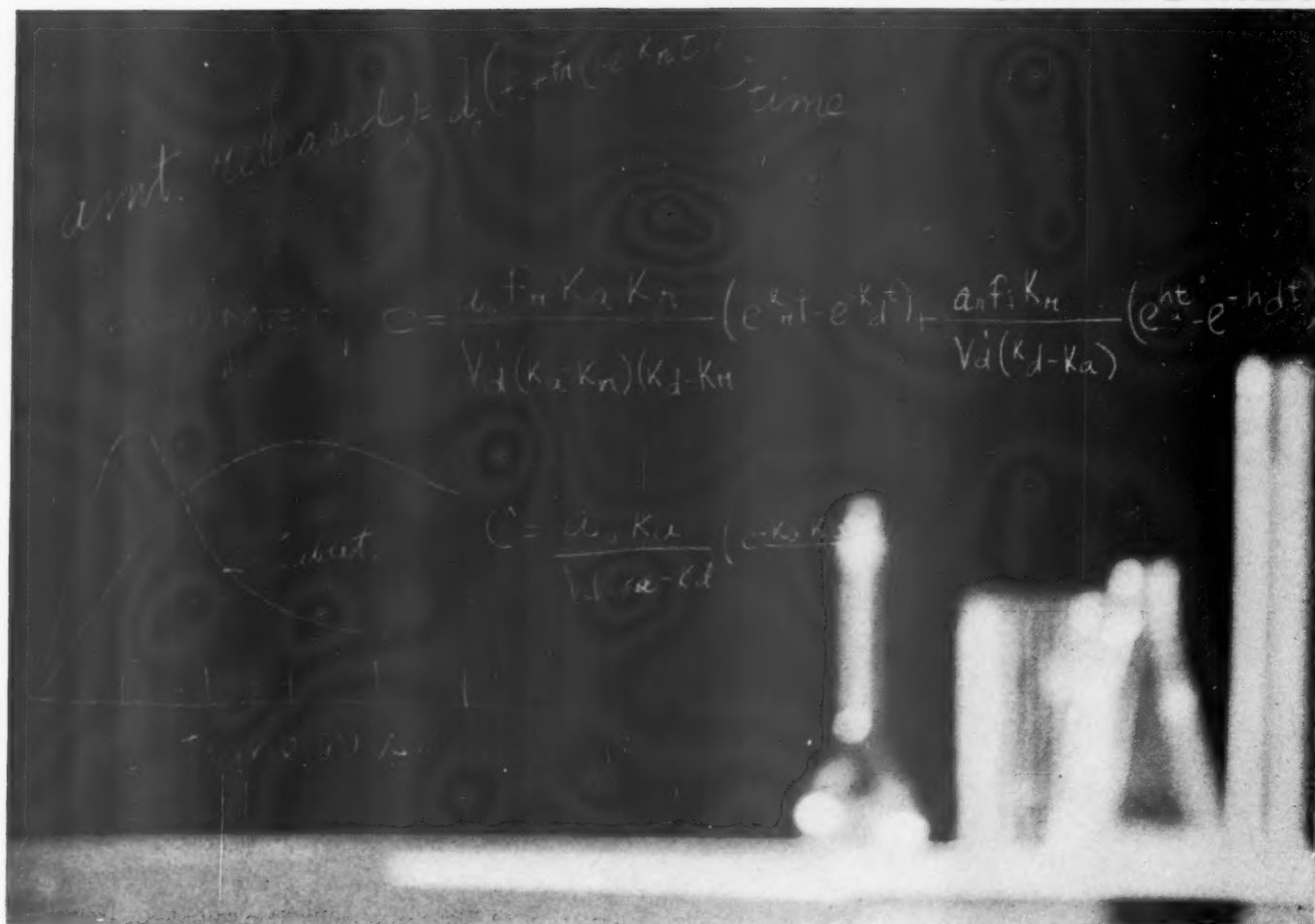
Dosage: A single inhalation at onset of headache. Additional inhalations should be spaced not less than 5 minutes apart. Not more than 6 inhalations in any 24-hour period.

In 2.5 cc. stainless steel vial (50 doses) with plastic oral adapter. Each depression of metering valve delivers 0.36 mg. ergotamine tartrate self-propelled from the oral adapter.



Northridge, California

DESBUTAL GRADUMET



A Release Pattern So Predictable you can actually plot it as a mathematical equation

Smooth . . . steady . . . sustained.
This is the Gradumet® Principle in action.
And it's a mathematical fact: *In laboratory tests, the release pattern of this ingenious, new vehicle is so precise it can be expressed as an equation.*

Studies indicate that you can expect the same pattern of release in actual clinical use. In the case of new Desbutal® Gradumet, the coordinated effect of the component drugs—Desoxyn® and Nembutal®—continues throughout the day—to elevate the mood, to calm the patient, to

establish a feeling of confidence.

Indicated for anorectic effect in obesity; also for counteracting depression associated with anxiety, and tension in psychosomatic disorders, neuroses, mild psychoses and other conditions. Usual all-day dosage is one Desbutal Gradumet. In two strengths, Desbutal 10 Gradumet (10 mg. of Desoxyn and 60 mg. of Nembutal) and Desbutal 15 Gradumet (15 mg. of Desoxyn and 90 mg. of Nembutal). Bottles of 100 and 500.



®DES OXYN—METHAMPHETAMINE HYDROCHLORIDE, ABBOTT.

®NEM BUTAL—PENTOBARBITAL, ABBOTT.

®GRADUMET—LONG-RELEASE DOSE FORM, ABBOTT; PAT. APPLIED FOR.

010-286

even if your patient is a whip snapper*
he'll soon be riding high again, thanks to

PARAFON[®]

(PARAFLEX[®] + TYLENOL[®])

for muscle relaxation plus analgesia

in arthritis

PARAFON[®] with Prednisolone

McNEIL

McNeil Laboratories, Inc.
Philadelphia 32, Pa.

prescribe PARAFON in low back pain—sprains—
strains—rheumatic pains

Each PARAFON tablet contains:

PARAFLEX[®] Chlorzoxazone† 125 mg.

The low dosage skeletal muscle relaxant

TYLENOL[®] Acetaminophen 300 mg.

The superior analgesic in musculoskeletal pain

Dosage: Two tablets t.i.d. or q.i.d.

Supplied: Tablets, scored, pink, bottles of 50.

Each PARAFON with Prednisolone tablet contains:

PARAFLEX[®] Chlorzoxazone† 125 mg., TYLENOL[®]

Acetaminophen 300 mg., and prednisolone 1.0 mg.

Supplied: Tablets, scored, buff colored, bottles of 36.

Dosage: One to two tablets t.i.d. or q.i.d.

Precautions: The precautions and contraindications
that apply to all steroids should be kept in mind
when prescribing PARAFON with Prednisolone.

*tailman on hook-and-ladder fire engine

†U.S. Patent No. 2,895,877

316A60



DESBUTAL GRADUMET



A Release Pattern So Uniform

**it works the same in the presence of G. I. fluids,
distilled water or tomato juice**

An odd test? Consider the results. Desbutal® Gradumet® was added to solutions ranging from pH 1.2 to pH 7. The tomato juice was included partly because of its viscosity, partly because of its acid pH and partly because we wanted to see what would happen. Analytical determinations were made at hourly intervals.

The result? In every case, a uniform release pattern was evidenced. Which points up one of the important characteristics of new Desbutal Gradumet:

Individual differences in gastro-intestinal secretions, enzymes or motility in no way influence amount or duration of drug release. The active ingredients—Desoxyn® and Nem-

butal®—are leached from the Gradumet at a measured rate over the day. And at day's end—the empty Gradumet is excreted harmlessly in the stool.

Indicated for anorectic effect in obesity; also for counteracting depression associated with anxiety, and tension in psychosomatic disorders, neuroses, mild psychoses and other conditions. Usual all-day dosage is one Desbutal Gradumet. In two strengths, Desbutal 10 Gradumet (10 mg. of Desoxyn and 60 mg. of Nembutal) and Desbutal 15 Gradumet (15 mg. of Desoxyn and 90 mg. of Nembutal). Bottles of 100 and 500 tablets.



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©NEMBUTAL—PENTOBARBITAL, ABBOTT.
©GRADUMET—LONG-RELEASE DOSE FORM, ABBOTT; PAT. APPLIED FOR.
D10-287

CONSISTENTLY GOOD
CLINICAL RESULTS
IN TRICHOMONAL
AND MONILIAL VAGINITIS

TRICOFURON IMPROVED (Suppositories and Powder)
cured 143 of 161 patients with vaginitis due to
Trichomonas vaginalis, *Candida (Monilia) albicans*,
or both. "Almost immediate symptomatic
improvement was noted with the first insufflation."

Criteria for cure: freedom from
infecting organisms as well as symptoms on
repeated examinations during a three-month follow-up
This cure rate of 88.8% is "surprisingly similar"
to results reported by earlier investigators.

Coolidge, C. W.; Glisson, C. S., and Smith, A. S.:
J.M.A. Georgia 48:167, 1959.

TRICOFURON®
IMPROVED

2-step treatment brings swift relief,
eradicates stubborn trichomonads,
Candida (Monilia) albicans,
Hemophilus vaginalis

1. **POWDER** for weekly insufflation in your office.
MICOFUR®, brand of nifuroxime, 0.5%
and FUROXONE®, brand of furazolidone, 0.1% in
an acidic water-dispersible base.

2. **SUPPOSITORIES** for continued home use
—1st week one suppository in the morning
and one on retiring. After 1st week, one
suppository at night may suffice.

Continue use of suppositories during menses.
Treatment should be continued throughout a complete
menstrual cycle and for several days thereafter.

MICOFUR 0.375% and FUROXONE 0.25%
in a water-miscible base.

*Rx new box of 24 suppositories with applicator
for more practical and economical therapy.*

*Also available:
box of 12 suppositories with applicator.*

NITROFURANS—a unique class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

(+)= DESBUTAL GRADUMET



A Release Pattern So Carefully Synchronized

each half releases its own drug in "harmony" to the other
(no more "peaks and dips")

With the precision of a finely-made watch, the long-acting Gradumet is timed to expel its drug contents throughout the day.

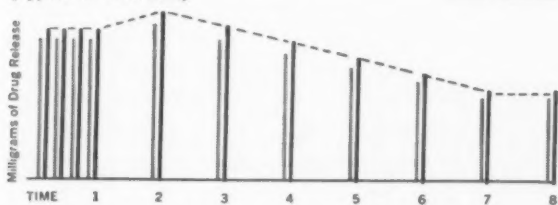
Desbutal® Gradumet® consists of two halves (Desoxyn® and Nembutal®, each in its own matrix) which are fused to form an inseparable, single tablet. Each half is specially-engineered with its own release rate

to insure that the combined effect is harmonious in onset and decline. See chart.

Note the absence of "spread" between the two drugs over the 8-hour period. This insures that an optimal ratio of the two ingredients will be made available to the patient at all intervals during the day.

Indicated for anorectic effect in obesity; also for counteracting depression associated with anxiety, and tension in psychosomatic disorders, neuroses, mild psychoses and other conditions. Usual all-day dosage is one Desbutal Gradumet. In two strengths, Desbutal 10 Gradumet (10 mg. of Desoxyn and 60 mg. of Nembutal) and Desbutal 15 Gradumet (15 mg. of Desoxyn and 90 mg. of Nembutal).

DESBUTAL RELEASE PATTERN — Desoxyn
(Typical in Vitro Test) — Nembutal



40% of the drug contents of the Desbutal Gradumet is leached out within the first hour. Release of remaining drugs continues during the following seven hours. Dotted line shows the smooth, steady release pattern.



NOW—for more comprehensive control of

*'pain
&
spasm'*

- pain due to or associated with
- spasm of skeletal muscle



a NEW  muscle relaxant-analgesic

Robaxisal[®]

ROBAXIN[®] WITH ASPIRIN

ROBAXISAL, a new dual-acting muscle relaxant-analgesic, effectively treats both skeletal muscle spasm and severe pain due to or associated with the spasm. Each Tablet contains:

- A relaxant component—Robaxin*—widely recognized for its prompt, long-lasting relief of painful skeletal muscle spasm, with unusual freedom from undesired side effects. 400 mg.
*Methocarbamol 'Robins' U.S. Pat. No. 2770649.
- An analgesic component—aspirin—whose pain-relieving effect is markedly enhanced by Robaxin, and which has added value as an anti-inflammatory and anti-rheumatic agent. . . (5 gr.) 325 mg.

SUPPLY: ROBAXISAL Tablets (pink-and-white, laminated) in bottles of 100 and 500.

Also available: ROBAXIN Injectable, 1.0 Gm. in 10-cc ampul. ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50 and 500.

... or when anxiety accompanies pain and spasm: **ROBAXISAL[®]-PH** (Robaxin[®] with Phenaphen[®]). Sedative-enhanced analgesic and skeletal muscle relaxant. Each two white-and-green laminated ROBAXISAL-PH tablets contain: methocarbamol 800 mg., plus the equivalent of one Phenaphen capsule (phenacetin 194 mg., acetylsalicylic acid 162 mg., hyoscyamine sulfate 0.031 mg., and ¼ gr. phenobarbital 16.2 mg.). Bottles of 100 and 500.

A. H. ROBINS CO., INC., Richmond 20, Va.

Making today's medicines with integrity
... seeking tomorrow's with persistence

**(+)= DESBUTAL
GRADUMET**



A Release Pattern So Subtle

your "nervous eater" will scarcely know she's taken "medicine"
(except in her bright, new feeling of confidence)

Ask your patient for a report within a few days. Check her appetite . . . see if she doesn't feel calmer, more optimistic. Especially, look for the absence of unwanted drug effects.

You can expect these good results because the release rate of new Desbutal® Gradumet® is so ingeniously timed that "jolts" or "dips" are practically impossible. Approximately 40% of the component drugs (Desoxyn® and Nembutal®) is released during the first hour; thereafter, release continues at a rate roughly 8% per hour. Your patient gets medication at all

times—but so smoothly and subtly that she'll never be conscious of an undesired "drug effect."

Indicated for anorectic effect in obesity; also for counteracting depression associated with anxiety, and tension in psychosomatic disorders, neuroses, mild psychoses and other conditions. Usual all-day dosage is one Desbutal Gradumet. In two strengths, Desbutal 10 Gradumet (10 mg. of Desoxyn and 60 mg. of Nembutal) and Desbutal 15 Gradumet (15 mg. of Desoxyn and 90 mg. of Nembutal) Bottles of 100 and 500.

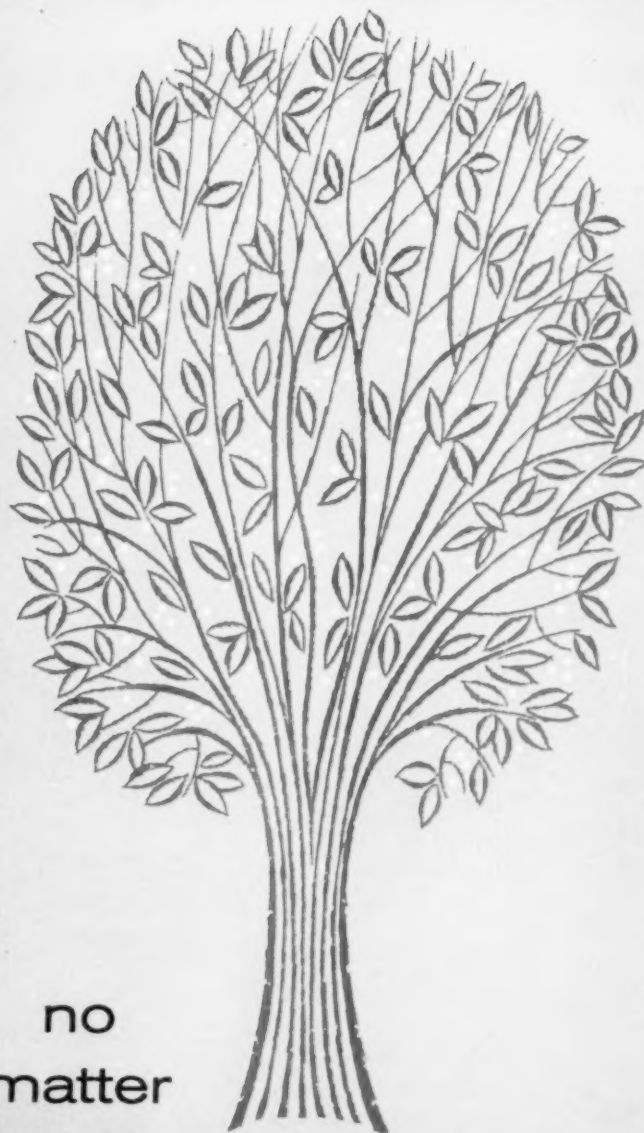
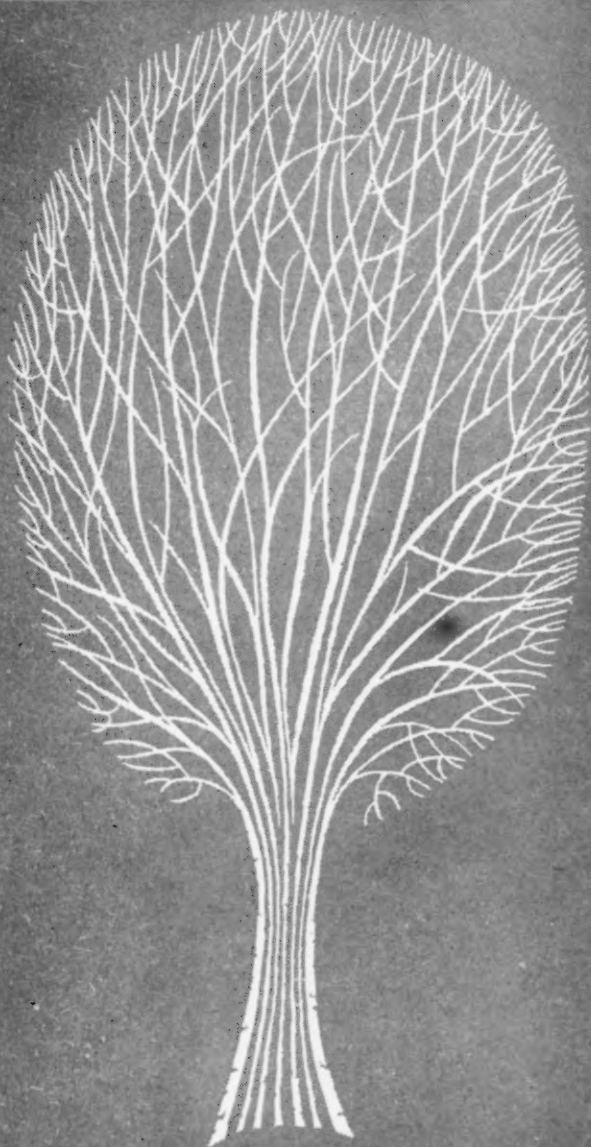


® DESOXYN—METHAMPHETAMINE HYDROCHLORIDE, ABBOTT.

® NEMBUTAL—PENTOBARBITAL, ABBOTT.

® GRADUMET—LONG-RELEASE DOSE FORM, ABBOTT; PAT. APPLIED FOR.

Q10 109



no
matter
what
the
season

DECLO

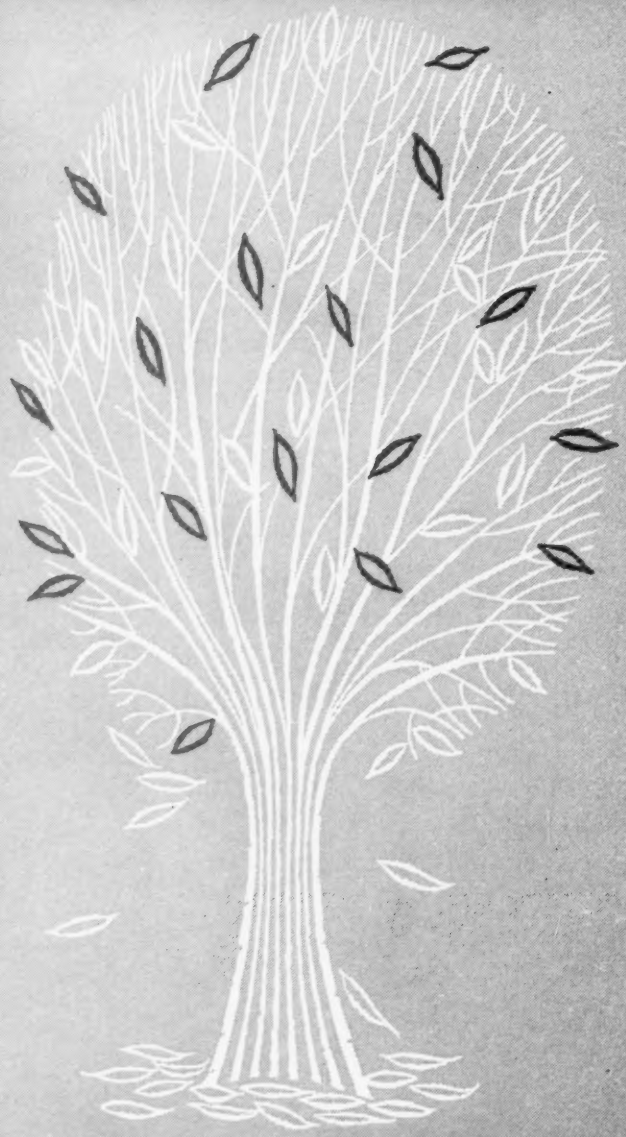
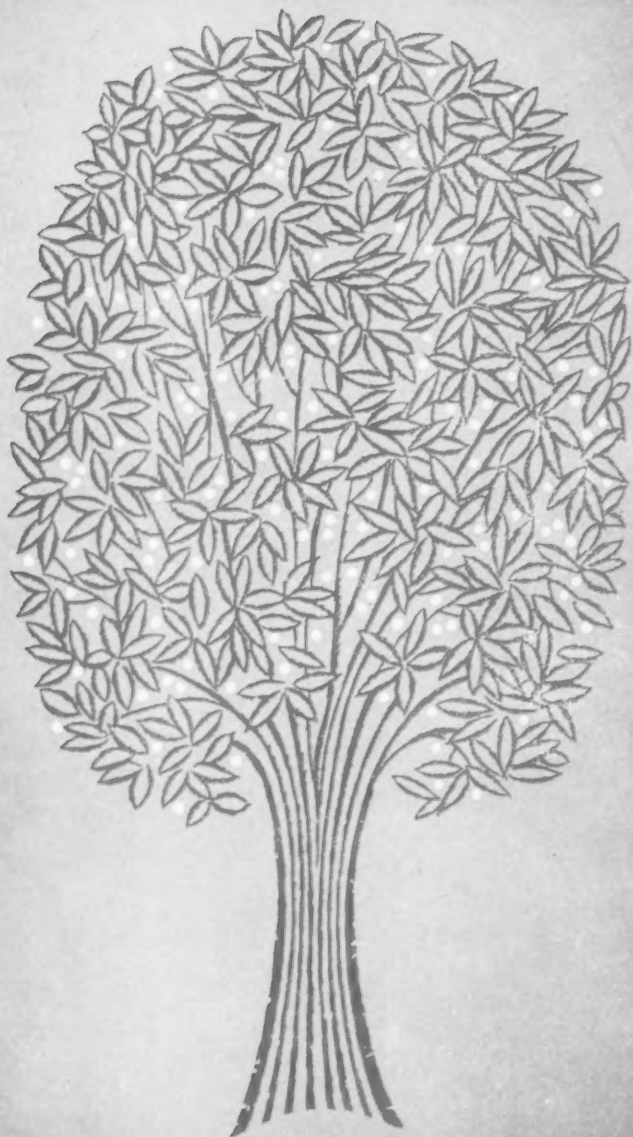
FULL OR GREATER *IN VIVO* ACTIVITY—effective control in a wide range of infections

SUSTAINED ACTIVITY LEVELS—greater stability in body fluids, prolonged retention, resistance to

Capsules, DECLOMYCIN *Demethylchlortetracycline* 150 mg., bottles of 16 and 100. *Dosage:* average adult, 1 capsule four times daily.

Pediatric Drops, DECLOMYCIN *Demethylchlortetracycline* 60 mg./cc. (custard flavor) in 10 cc. bottle with calibrated dropper. *Dosage:* 1-2 drops (3-6 mg.) per pound body weight per day—divided into 4 doses.

LEDERLE LABORATORIES



MYCIN[®]



Demethylchlortetracycline Lederle

degradation . . . continued effect on interruption of dosage

"EXTRA-DAY" ACTIVITY—protects against relapse or secondary bacterial attack after stopping dosage

New Syrup, Cherry-Flavored, DECLOMYCIN Demethylchlortetracycline 75 mg./5 cc. teaspoonful in 2 oz. bottle.
Dosage: 3-6 mg./lb./day—divided into 4 doses.

Precautions: The use of antibiotics occasionally may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential.

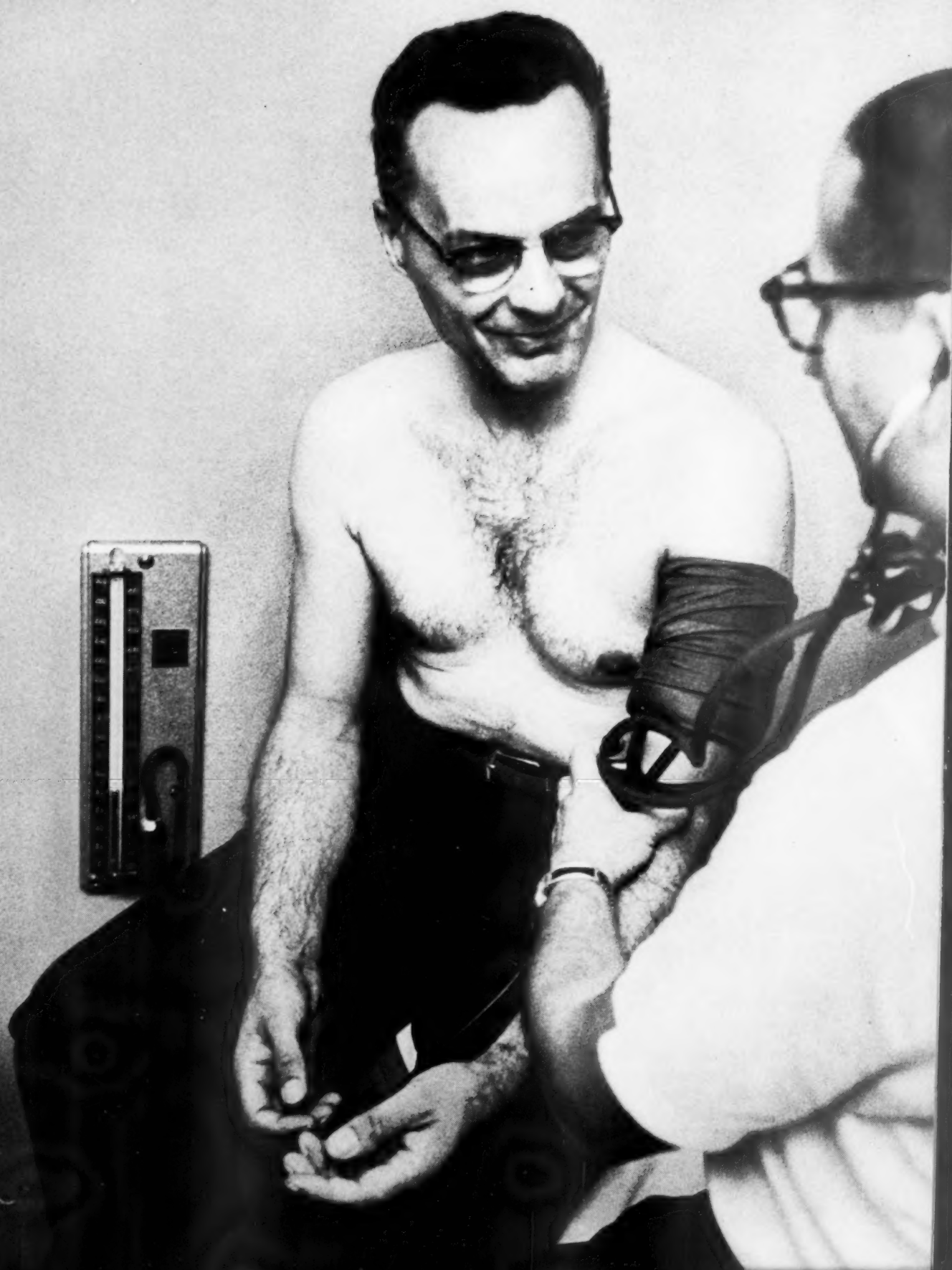
a Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.

Lederle

this hypertensive patient prefers Singoserp

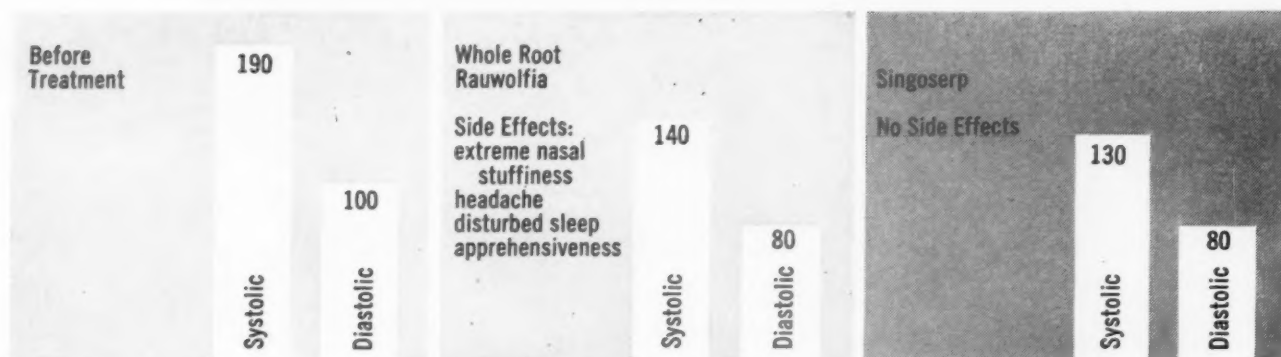
Patient's comment: "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all."

Photo used with patient's permission.



...and so does his physician

Clinician's report: J. M., a salesman, had a 16-year history of hypertension and was rejected by the U.S. Army because of high blood pressure. When treated with whole root rauwolfia, patient had satisfactory blood pressure response but could not tolerate side effects. Singoserp, in a dose of 0.5 mg. daily, not only reduced patient's blood pressure still further, but did not produce any side effects.



Many hypertensive patients and their physicians prefer Singoserp[®] because it usually lowers blood pressure without rauwolfia side effects

SUPPLIED: Singoserp Tablets, 1 mg. (white, scored). Also available: Singoserp[®]-Esidrix[®] Tablets #2 (white), each containing 1 mg. Singoserp and 25 mg. Esidrix; Singoserp[®]-Esidrix[®] Tablets #1 (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix.

Complete information sent on request.

Singoserp[®] (syrosingopine CIBA)
Singoserp[®]-Esidrix[®] (syrosingopine and hydrochlorothiazide CIBA)

C I B A
SUMMIT, NEW JERSEY

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For the most advanced Fluid Therapy

Amsco

- ◆ Parenteral Solutions...
- ◆ Blood and Plasma Bottles
- ◆ Disposable Administration Sets —

Amsco parenteral solutions and administration equipment provide medical and nursing staffs with complete and dependable facilities for every fluid therapy need.

Flawless purity, prescription accuracy and rigid non-pyrogenic qualities are, of course, minimum requirements for all injectionables. To these, however, *Amsco* adds "plus" factors of completeness of line, ease and speed of handling and prompt service which are of genuine benefit to every hospital.

Amsco Laboratories representatives are well informed on the most current fluid therapy techniques, and the current findings of *Amsco* Research. Service offices and warehouse stocks are strategically located to speed consultation and service.

For detailed literature, request Brochure MC-512R3

- ◆ Parenteral and Surgical Solutions
- ◆ Blood Transfusion and Plasma Bottles
- ◆ Pressurized Blood Transfusion Set — "460"
- ◆ Plasma Volume Expander (Plavolex)
- ◆ Disposable Administration and Donor Sets
- ◆ A fully modern Sterile Fluids concept for hospital prepared solutions

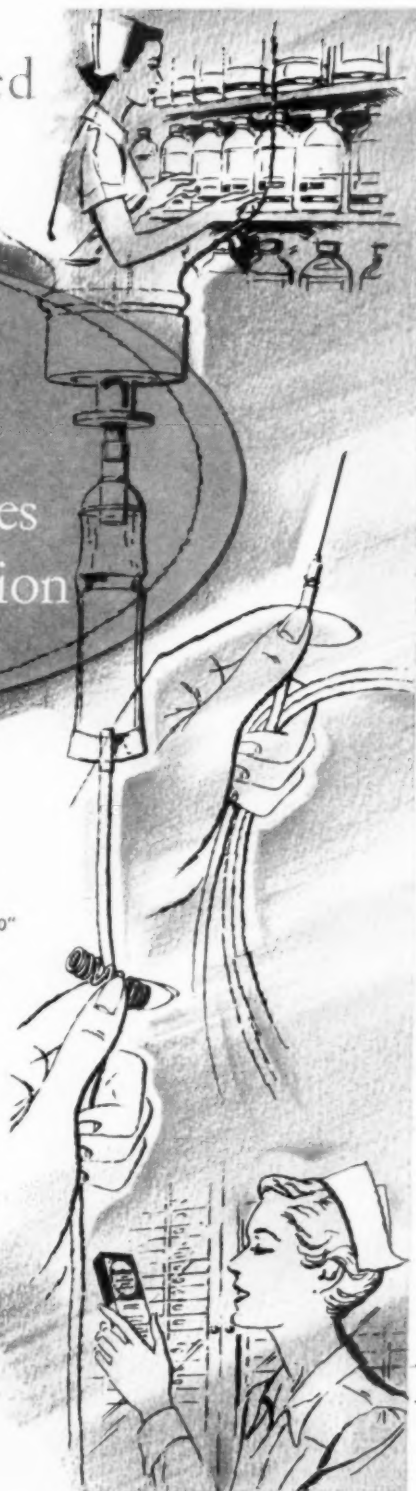


AMSCO
LABORATORIES

BRIDGEMAN, PENNSYLVANIA

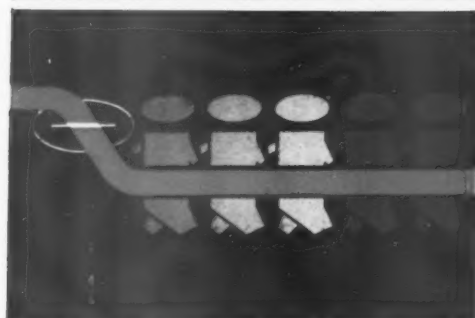
World's Largest Designer and
Manufacturer of Sterilizers, Surgical
Tables, Lights and related equipment
and supplies

DIVISION OF AMERICAN STERILIZER COMPANY



*making
oral blood-sugar
control a reality
for more
diabetics*

Diabinese®
brand of chlorpropamide



*Science
for the world's
well-being™*

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, **DIABINESE** often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

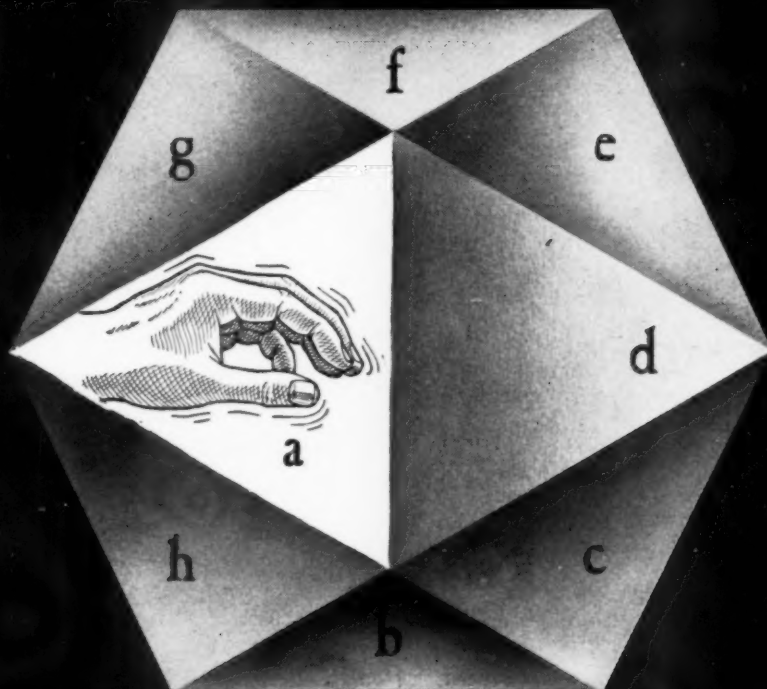
SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, **DIABINESE** should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since **DIABINESE** is not significantly metabolized and is excreted slowly. **DIABINESE** as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. **DIABINESE** may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on **DIABINESE** drink alcoholic beverages.

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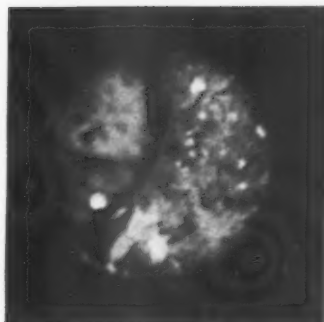
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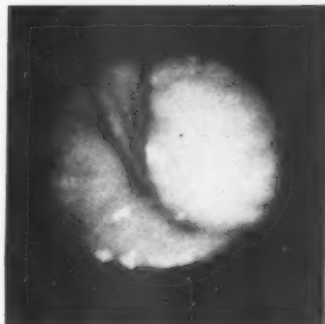
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Excellent results in ulcerative colitis even where other steroids have failed

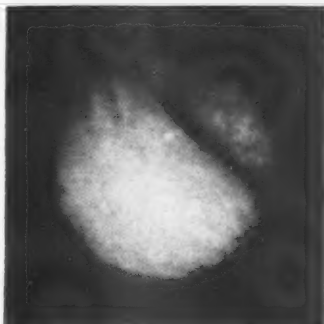
*Proctoscopic view
of the sigmoid
in acute stage
of ulcerative
colitis*



*Proctoscopic view
of the sigmoid
following
Depo-Medrol
retention enemas
for acute stage
of ulcerative
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*Proctoscopic view
of sigmoid colon
in a normal person*

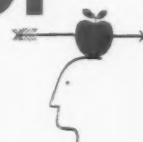


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The results obtained were 76 per cent excellent; 11 per cent fair. In cystitis of short duration and without urinary obstruction 100 per cent good results were reported. average dosage: 3 Gm./day for 2 weeks

in pathologic conditions that cannot be cured 38 cases of chronic urinary tract infection:² "The cause of the infection in 25 cases was residual urine due to lower urinary tract disease, which for some reason could not be eliminated, such as prostatic carcinoma or hypertrophy (16 cases), vesical diverticulum or hypotonia (6 cases). Chronic upper urinary tract infection was present in 22 cases, some of which were secondary to the lower tract obstructive lesions."

"The results of treatment were as follows: Good, 17 cases, urine became clear and symptoms subsided while under treatment; fair, 10 cases, infection reduced and symptoms became less or subsided; poor, 11 cases, no evident change in urine or symptoms." initial dosage: 2 Gm./day

52 paraplegics with g.u. infections:³ "Urinalysis reverted to normal in 53 per cent of the 'Thiosulfil' group . . ."

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The Sulfa Compound Used Successfully Without Interruption for: one month;^{3,4} more than 6 weeks;² 90 days;⁵ 18 months;³ 5 to 6 years.⁷

DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day ¹
2 weeks to 3 months	2 Gm./day ^{3,4}
3 months or longer	0.5 Gm./day ⁷

Suggested Range of Dosage: 1 or 2 tablets three or four times daily. **Note:** The usual precautions exercised with sulfonamides should be observed. **Supplied:** No. 786—Bottles of 100 and 1,000 scored tablets. Each tablet contains 0.5 Gm. sulfamethizole.

References—1. Bourque, J.-P., and Gauthier, G.-E.: Seven years' experience with sulfamethizole, to be published. 2. Barnes, R. W.: *J. Urol.* 71:655 (May) 1954. 3. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: *Rocky Mountain M. J.* 56:66 (Mar.) 1959. 4. Bourque, J.-P., and Joyal, J.: *Canad. M.A.J.* 68:337 (Apr.) 1953. 5. Hughes, J., Coppridge, W. M., and Roberts, L. C.: *South. M. J.* 47:1082 (Nov.) 1954. 6. Goodhope, C. D.: *J. Urol.* 72:552 (Sept.) 1954. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: *North Carolina M. J.* 17:320 (July) 1956.

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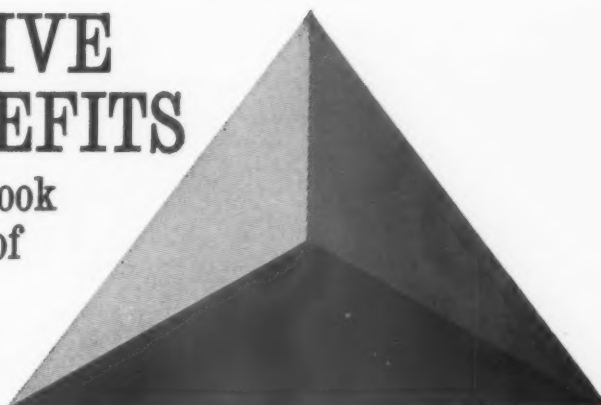
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1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

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1. Blumberg, N. *et al.*: *Fed. Proc.* 17:351, March 1958. 2. Boyd, L. J. *et al.*: *Am. J. Cardiol.* 3:229, Feb. 1959. 3. Brick, H. *et al.*: *J. Social Therapy* 4:190, 1958. 4. Bulla, J. D. *et al.*: *Am. Pract. & Digest Treat.* 10:1961, Nov. 1959. 5. Ewing, J. A. and Haizlip, T. M.: *Am. J. Psychiat.* 114:835, March 1958.

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11. Lasagna, L.: J. Chron. Dis. 3:122, Feb. 1956. 12. Muhlfelder, W. J. et al.: Dis. Nerv. System 20:587, Dec. 1959. 13. Pollak, M.: Practitioner 184:231, Feb. 1960. 14. Rickels, K. et al.: J.A.M.A. 171:1649, Nov. 21, 1959. 15. Russek, H. I.: Am. J. Cardiol. 3:547, April 1959. 16. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

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Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, as indicated by prothrombin time determinations.

1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Publ., Mar., 1960, p. 13.

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References: (1) Goodier, T. E. W., & Parry, W. R.: *Lancet* 1:356, 1959. (2) Modarress, Y.; Ryan, R. J., & Francis, Sr. C.: *J. M. Soc. New Jersey* 57:168, 1960. (3) Petersdorf, R. G., et al.: *Arch. Int. Med.* 105:398, 1960. (4) Rebhan, A. W., & Edwards, H. E.: *Canad. M.A.J.* 82:513, 1960. (5) Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* 173:475, 1960. (6) Olarte, J., & de la Torre, J. A.: *Am. J. Trop. Med.* 8:324, 1959. (7) Berle, B. B., et al.: *New York J. Med.* 59:2383, 1959. (8) Fisher, M. W.: *Arch. Int. Med.* 105:413, 1960.

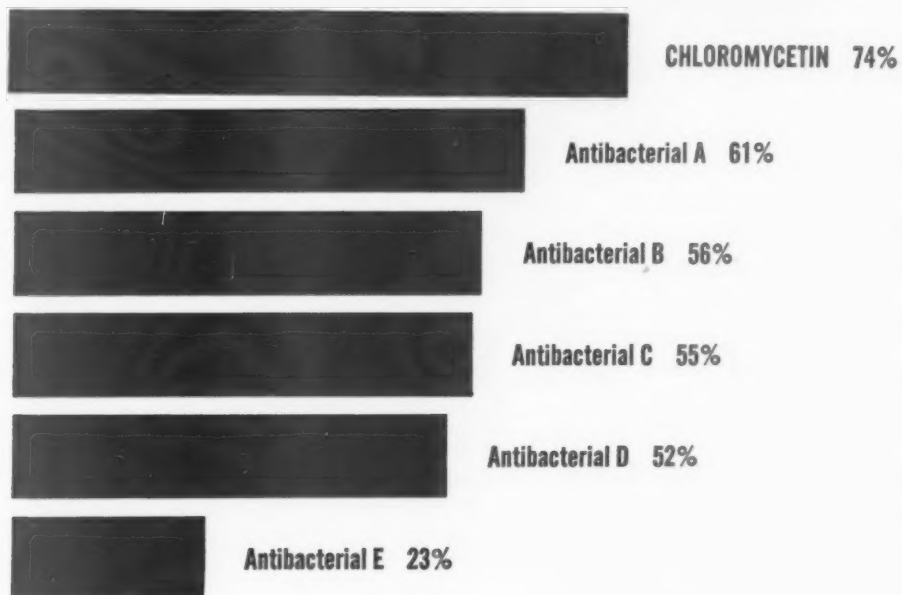
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"... our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, 3:199, (Feb.) 1959.



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in cirrhosis with ascites

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., 103:415, (March) 1959.




in renal edema

"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., 103:369, (March) 1959.



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potentiated therapy for mild to moderate hypertension

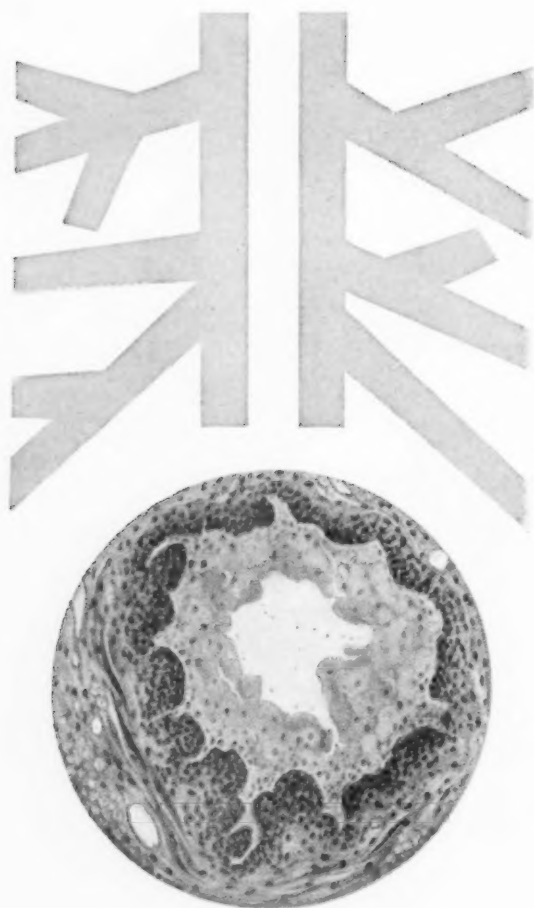
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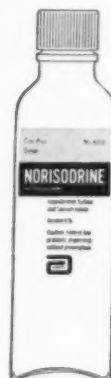
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¹Frohman; I. P.; Washington, D.C.: communication to the Medical Department, Abbott Laboratories, Jan. 16, 1960.

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Clearing of Tinea barbae, caused by *Trichophyton verrucosum*, after five weeks of oral therapy.

Photo courtesy of James M. Flood, M.D., Sayre, Pa.

S-597



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IN BRIEF

Vistaril® HYDROXYZINE HYDROCHLORIDE **Parenteral Solution**

Vistaril is a rapid-acting calmative with a wide margin of safety. Its use preoperatively generally permits a reduction in dosage of narcotics and barbiturates. Vistaril's antiemetic properties further enhance its usefulness pre- and post-operatively.

ACTIONS & INDICATIONS: Vistaril, as part of a preoperative regimen, can safely relax your patients by allaying fear and apprehension.

ADVANTAGES: Vistaril produces a calming effect without hypnosis. Vistaril provides direct and secondary muscle relaxation. Vistaril apparently is non-addicting — discontinuance after months of treatment has not produced withdrawal symptoms. Vistaril has a remarkable record of safety, when used in recommended dosage. Unlike the phenothiazines, parkinsonism and blood or liver toxicities have not been reported with Vistaril. Unlike the rauwolfia derivatives, Vistaril acts rapidly, does not increase gastric secretions, and there have been no reports of nasal congestion, drug-induced depression, or sinusitis associated with its use. Unlike the meprobamates, there have been no reports of incoordination, ataxia, abdominal discomfort, anorexia, nausea, vomiting, diarrhea, allergic dermatitis, or anaphylactic reactions. VISTARIL PARENTERAL SOLUTION permits rapid action and may be given via I.M. or I.V. routes.

CONTRAINDICATIONS: There are no known contraindications to Vistaril.

SIDE EFFECTS AND PRECAUTIONS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing upon reduction of dosage or within a few days of continued therapy. Dryness of mouth may be encountered at higher dosages. The potentiating action of hydroxyzine must be taken into consideration when it is used in conjunction with C.N.S. depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is for 24-48 hours, unless changed by judgment of physician.

ADMINISTRATION AND DOSAGE: Vistaril dosage varies with the state and response of each patient, rather than on a weight basis. Dosage should be individualized by the physician for optimum results. The usual parenteral dosage in preoperative sedation for adults is 25-50 mg. I.M. or I.V. q. 4 h., p.r.n., (alone or in conjunction with reduced dosages of narcotics); for children, 0.5 mg./lb. body weight I.M.

HOW SUPPLIED: Vistaril Parenteral Solution—10 cc. vials and 2 cc. Steraject® Cartridges, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. Vistaril Capsules (as the pamoate)—25, 50, and 100 mg. Oral Suspension (as the pamoate)—25 mg. per 5 cc. teaspoonful.

More detailed professional information available on request.

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

They can be separated

COMFORTABLE
PREOPERATIVE
SEDATION

FREQUENT
RESPIRATORY
DEPRESSION
AND HYPOTENSION

The use of narcotics alone in preoperative analgesia too often risks serious undesirable effects including respiratory depression and hypotension. Narcotics combined with phenothiazines may risk other untoward effects including jaundice and blood dyscrasia.

VISTARIL makes possible a substantial reduction in the amount of meperidine (or other narcotics) required for satisfactory analgesia. VISTARIL PARENTERAL SOLUTION (I.M. or I.V.) helps to provide desired sedation and control of emesis while virtually eliminating undesirable reactions.

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measured calories for adequate nutrition
with high satiety on 900 calories a day—
without appetite depressants

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Metrecal *alone* is the *complete diet*. The daily ration provides 70 Gm. protein, 110 Gm. carbohydrate and 20 Gm. of fat plus vitamins and minerals to meet or exceed M.D.R.

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In three clinical studies,^{1,2,3} overweight subjects showed weight losses averaging over 1/2 pound per day/per patient during the initial weeks. There were no significant complications even when overweight was accompanied by other serious disorders.³ The excellent patient cooperation noted^{1,2,3} was attributed to hunger satisfaction, simplicity of use, palatability, and good tolerance.

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references:

- (1) Antos, R. J.: The Use of a New Dietary Product (Metrecal) For Weight Reduction, *Southwestern Med.* 40:695-697 (Nov.) 1959. (2) Tullis, I. F.: Initial Experience with a Simple Weight Control Formula, to be published. (3) Roberts, H. J.: Effective Long-Term Weight Reduction—Experiences With Metrecal, to be published.



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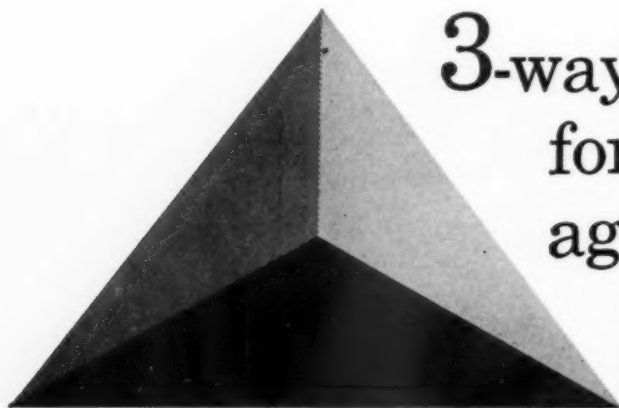
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specific treatment for arthritic joints

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□ **good to excellent response in a vast majority of patients**—"Low doses...provided rapid and effective relief...in almost all of the 157 patients treated..."¹ "...appeared to be superior as an intra-articular injectable substance to anything hitherto available."²

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□ **rapid relief of pain, swelling, and improved range of motion**—"Pain was relieved in 3 or 4 days, or less..."³ "...marked improvement in range of motion occurred in all of these patients."³ "...more potent, milligram for milligram, than other injectable corticosteroids."⁴

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Dosage: usual doses—2.5 to 5.0 mg. for smaller joints; 5.0 to 15.0 mg. for larger joints. *Side Effects:* outstandingly rare; although systemic effects do not ordinarily occur with Kenalog Parenteral when the proper techniques and dosages are used, careful clinical supervision is advisable for all patients receiving steroid therapy. *Contraindications:* infections in or near joints—e.g., gonococcal or tuberculous arthritis. *Supply:* a sterile aqueous suspension in 5 cc. vials, each cc. providing 10 mg. triamcinolone acetonide. *References:* 1. Sperling, I. L.: Clinical Research Notes vol. 3, No. 1 (Jan.) 1960. 2. Steinberg, C. L.: op. cit. 3. Urist, M. R.: op. cit. 4. Meltzer, L. E.: op. cit. 5. Schwartz, S.: op. cit. 6. Feltz, W. R.: op. cit.

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*Kestler, O.: Conservative Management of “Low Back Syndrome”,
J.A.M.A. 172: 2039 (April 30) 1960.*

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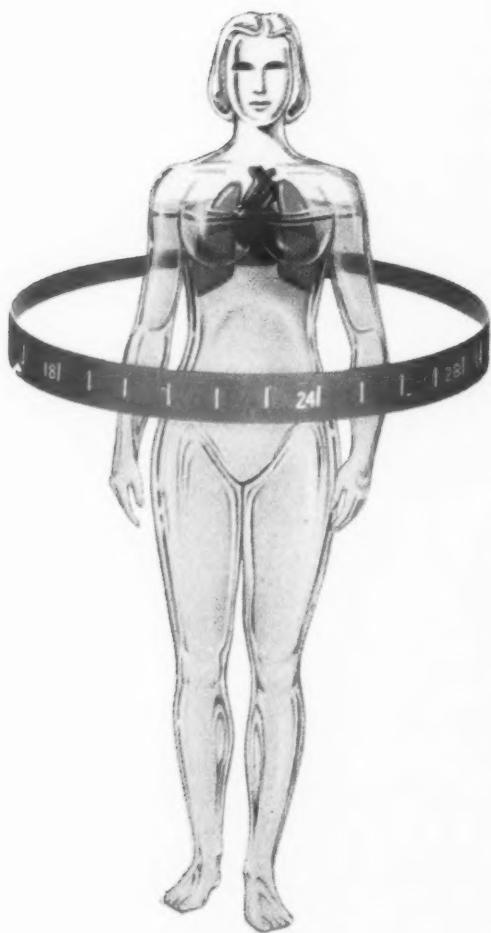
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clinicians report
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HYDROCHLOROTHIAZIDE

increased potency—without corresponding increase in side effects

*Fuchs, M. and Moyer, J.:
Diseases of the Chest 35:314, (March) 1959.*



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on the pathogenesis of pyelonephritis

"An inflammatory reaction here [renal papillae] may produce sudden rapid impairment of renal function. One duct of Bellini probably drains more than 5000 nephrons. It is easy to see why a small abscess or edema in this area may occlude a portion of the papilla or the collecting ducts and may produce a functional impairment far in excess of that encountered in much larger lesions in the cortex."¹

Recent experimental evidence in animals strongly supports the view that obstruction of the tubules in the medulla, as opposed to the cortex, predisposes the kidney to pyelonephritis,² and "... as few as 10 organisms injected into the medulla were capable of causing infection."³

The "exquisite sensitivity"⁴ of the medulla to infection highlights the importance of obstruction to the urine flow in the pathogenesis of pyelonephritis. "There is good cause to support the belief that many, perhaps most, cases of human pyelonephritis are the result of infection which reaches the kidney from the lower urinary tract."⁵

An agent, such as FURADANTIN, which has a specific affinity for the urinary tract and which is actively excreted by the cells of the tubules, as well as of the glomeruli,⁶ is particularly suited to meet the problems posed by the pathogenesis of pyelonephritis and the primary pathways of infection.

*in pyelonephritis
to eradicate the pathogens
no matter the pathway*

FURADANTIN[®]

brand of nitrofurantoin

*high urinary concentration
glomerular filtration
tubular excretion*

effective at glomerular and tubular levels: In addition to simple glomerular filtration, FURADANTIN is actively excreted by the tubule cells.

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broad bactericidal spectrum: FURADANTIN is bactericidal against a wide range of gram-positive and gram-negative bacteria including certain organisms resistant to other agents.

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well tolerated—even after prolonged use: FURADANTIN is nontoxic to kidneys, liver and blood-forming organs. No monilial superinfection, staphylococcal enteritis, proctitis or anovular pruritus has ever been reported.

no cross resistance or cross sensitization with other drugs: FURADANTIN, a synthetic nitrofurantoin, is unrelated chemically to any other class of antimicrobial drugs; cross resistance or cross sensitization does not occur.

AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. tablet q.i.d. with meals and with food or milk on retiring. **SUPPLIED:** Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Schreiner, G. E., *A.M.A. Arch. Int. M.* **102**:32, 1958. 2. Rocha, H., et al.: *Yale J. Biol. & Med.* **32**:120, 1959. 3. Freedman, L. R.: *Yale J. Biol. & Med.* **32**:272, 1960. 4. Freedman, L. R., and Beeson, P. B.: *Yale J. Biol. & Med.* **30**:406, 1958. 5. Rocha, H., et al.: *Yale J. Biol. & Med.* **30**:341, 1958. 6. Paul, M. F., et al.: *Am. J. Physiol.* **197**:580, 1959.



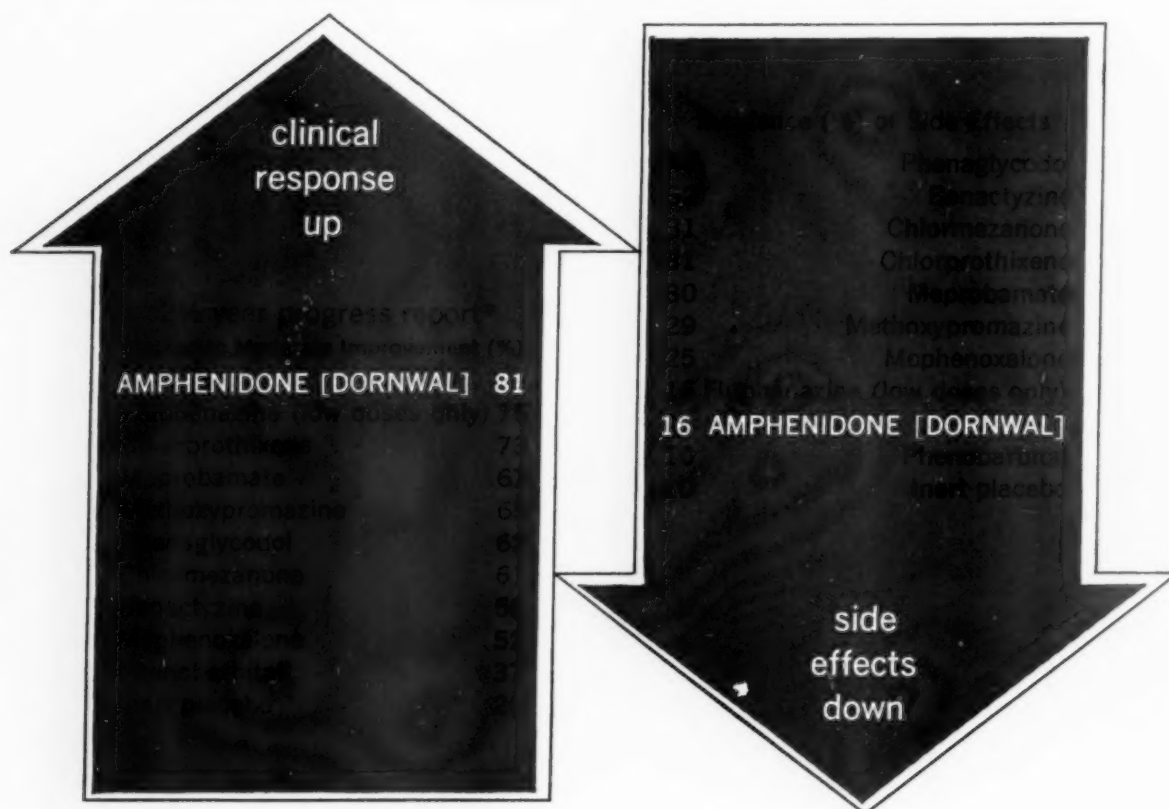
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Dose: Adults, one or two 200 mg. tablets three times a day. Children, 6 to 16, one or two 100 mg. tablets two times a day. Administration limited to three months duration.

*Nodine, J. H.; Bodi, T.; Slap, J.; Levy, H. A., and Siegler, P. E.: Human bioassay of tranquilizers in psychosomatic disorders, Scientific Exhibit, American Medical Association Annual Meeting, Miami Beach, Florida, June 13-17, 1960.

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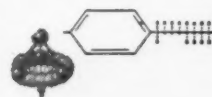
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March 1st, 1960: Large dilated stomach with incomplete pyloric obstruction. Etiology undetermined. Patient placed on "Murel"-S.A. — 2 tablets b.i.d. for one week — plus bland diet. No other medication.



March 10th, 1960: Stomach of normal size and tone. Large ulcer crater now visualized in the region of previously noted pyloric spasm and incomplete filling.

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prompt, continuous and prolonged antispasmodic action for 6 to 9 hours with a single tablet

"MUREL" Advantages¹⁻⁴

- Exceptionally effective clinically because three-way mechanism of action in one molecule (anticholinergic, musculotropic, ganglion-blocking) exerts synergistic spasmolytic effect
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"Murel" Injectable No. 405—10 mg. Valethamate bromide per cc.

Precautions: As with other antispasmodic agents, caution should be exercised in patients with prostatic hypertrophy, glaucoma, and in the presence of cardiac arrhythmias.

References available on request.



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Diagnosis: Hiatus hernia and gastric ulcer.



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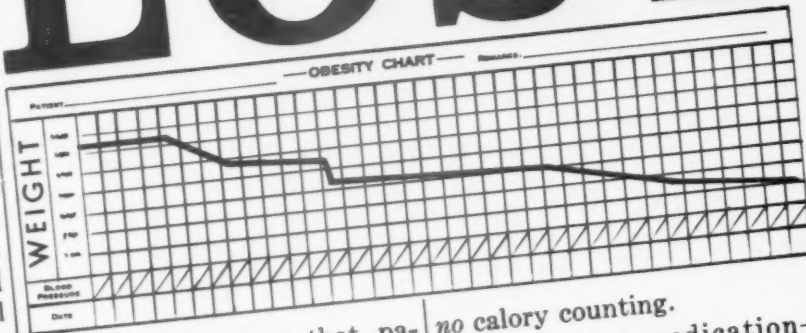
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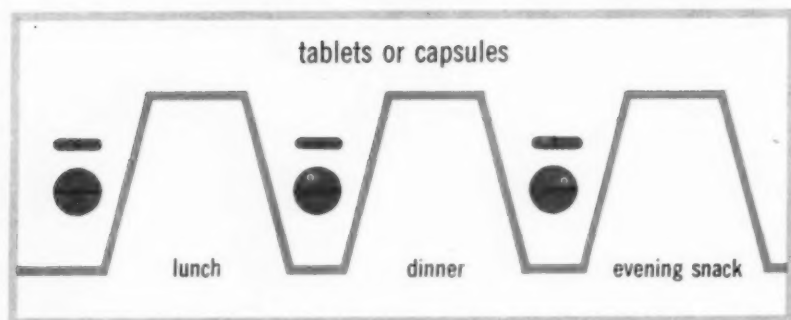
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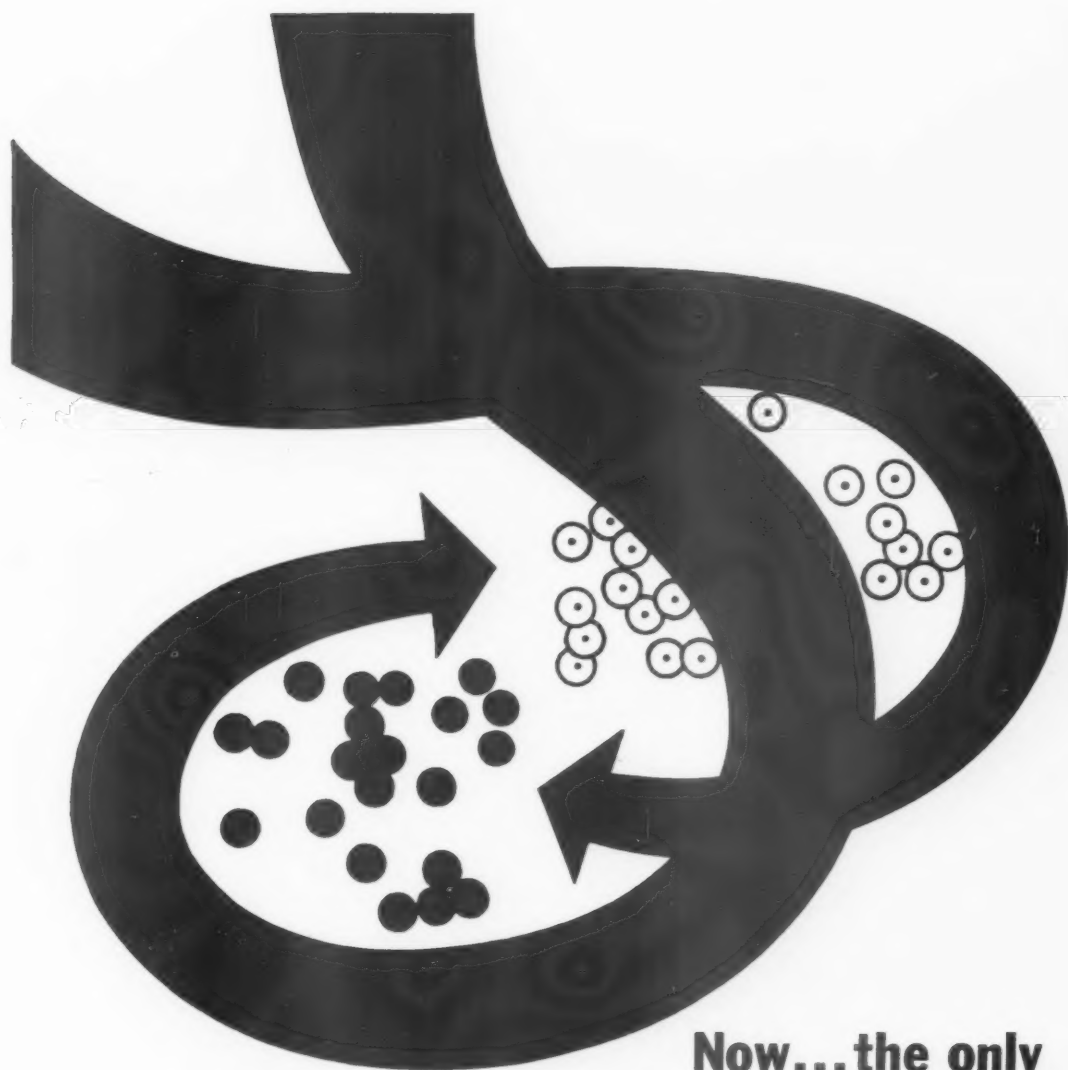
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with extra broad-spectrum benefits:— action at lower milligram intake... broad-range action... sustained peak activity... extra-day security against resurgence of primary infection or secondary invasion.

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CAPSULES, 150 mg. DECLOMYCIN Demethylchlortetracycline HCl
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DOSAGE: average adult, 1 capsule four times daily.

**LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY,
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how does Mellaril differ from other potent tranquilizers?



Mellaril[®]

THIORIDAZINE HCl
specific, effective tranquilizer



*provides highly effective tranquilization,
relieves anxiety, tension, nervousness,
but is virtually free of such toxic effects as*

jaundice

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*greater specificity of tranquilizing
action results in fewer side effects*



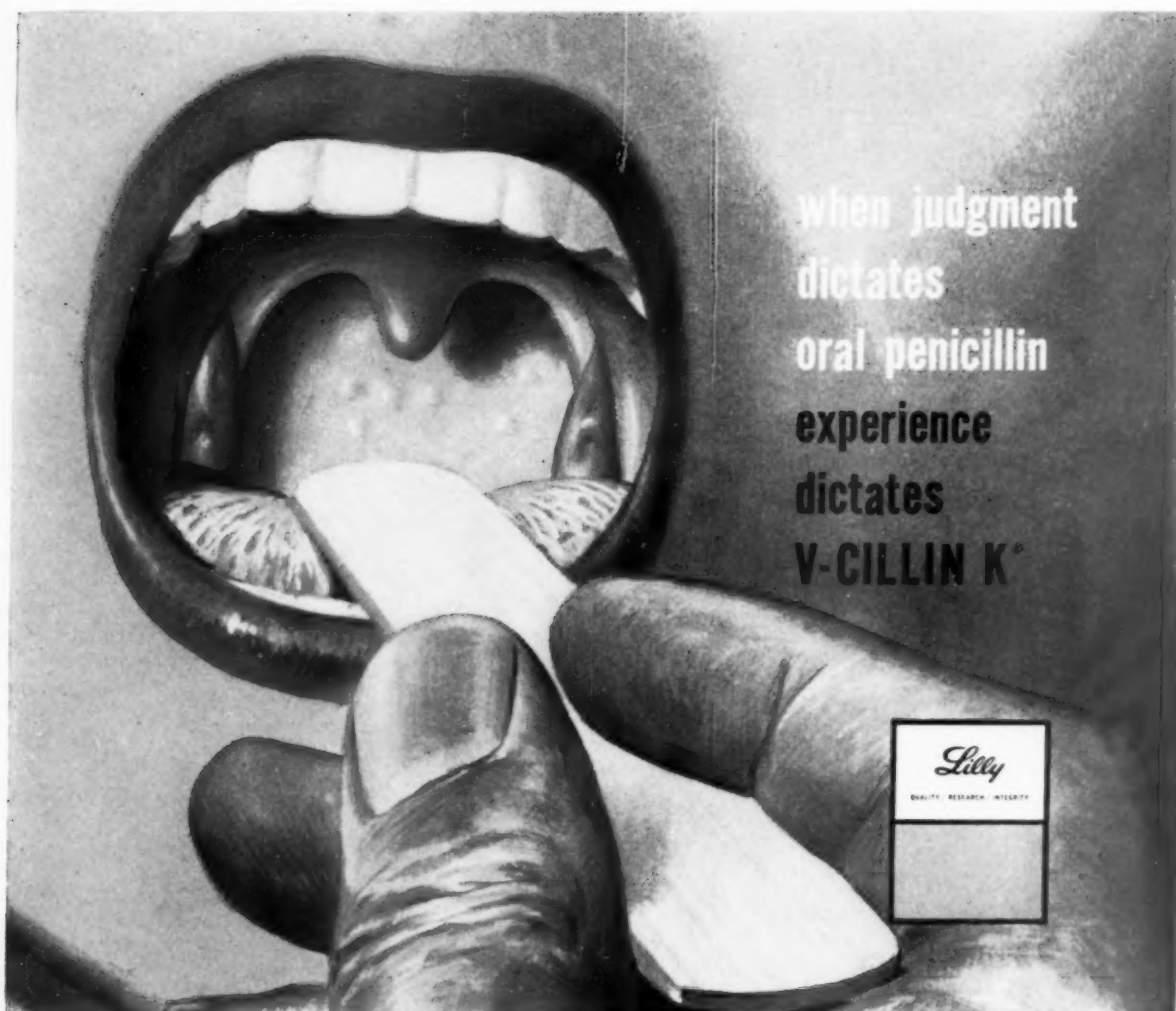
Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action — divorced from such "diffuse" effects as anti-emetic action.

"A new phenothiazine derivative, thioridazine [Mellaril®], was used to treat 71 patients, most of whom were unduly agitated and disturbed due to hospitalization for medical or surgical conditions....The response to treatment was considered satisfactory in 83.4 per cent of patients....In agreement with the published results of other investigators, we believe that thioridazine shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines."*

Supply: MELLARIL Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

*David, N. A.; Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a New Phenothiazine, In The Hospitalized Patient, A. M. & C. T. 7:364 (June) 1960.





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1. Griffith, R. S.: Comparison of Antibiotic Activity in Sera Following the Administration of Three Different Penicillins, *Antibiotic Med. & Clin. Therapy*, 7:No. 2 (February), 1960.

V-CILLIN K® (penicillin V potassium, Lilly)

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The American Journal of Medicine

VOL. XXIX

OCTOBER, 1960

No. 4

Editorial

A View of Gout as Inborn Error of Metabolism

THE heritable nature of gout has been recognized since the time of Galen, and gout has long been considered a disorder of metabolism possessing the vague attributes of a "diathesis" [1], but only comparatively recently has it been securely placed in the category of inborn errors of metabolism. Apparently it was the redoubtable Sir Archibald Garrod who first so classified gout [2], in 1931, almost twenty-five years after his initial announcement of the concept of inborn errors of metabolism [3]. This hesitancy was due to reservations expressed [2] in what may prove to be a prescient speculation, that gout "cannot be looked upon as due, like other such errors, to a rare mutation which occasionally occurs *de novo*, but rather as based upon an alternative and slightly divergent path of metabolism met with in a large part of the total population."

Once gout is viewed as a proper inborn metabolic error, akin to others of this genre, its peculiarities can be contemplated with enlarged perspective and increased insight. For one thing, the natural history of gout can now be shown to conform to what is already a well defined, repetitive clinical and metabolic pattern, familiar in other familial diseases. For another, the realization that all inborn errors of metabolism have in common a defect in protein biosynthesis, in particular in biosynthesis of a critical enzyme, may provide an important clue to the pathophysiology of gout, still all too obscure.

Primary (Inborn) Versus Secondary (Acquired) Gout. These considerations apply at least to primary

gout, the classic form of the disease, for there appears also to be an acquired or secondary form of gout. This is a complication particularly of hemopoietic disorders such as polycythemia vera and myeloproliferative diseases, in which the metabolic anomaly may be mimicked by augmented turnover of nucleic acids, with overproduction of purines including uric acid; and occasionally accompanied by the appearance of tophaceous deposits and acute arthritis responsive to colchicine [4,5]. Characteristic clinical and metabolic aberrations of many other inborn errors of metabolism may be duplicated by abnormalities arising in the course of unrelated diseases; for example, the inherited and acquired forms of "a" gammaglobulinemia [6], hemochromatosis [7], diabetes insipidus [8], methemoglobinemia [9], hyperlipemia [10], spherocytosis [11], to cite but a few.

Latent and Manifest Primary Gout. A familial incidence of secondary gout does not, by definition, occur. Even in primary gout a history of familial occurrence has been recorded in this country only in 6 to 18 per cent of cases [12]. However, epidemiological surveys of the familial segregation of hyperuricemia reveal a broader distribution of the inherited abnormality (an incidence of about 25 per cent in most series [13]), more pronounced and more frequent in male members. Like other inborn errors [14-16], there are more clinically inapparent than apparent carriers of the gouty trait; penetrance of the presumed autosomal dominant is variably in-

complete in different families; and expressivity in overt cases ranges from relatively early appearance of fulminant disease to long delayed emergence of mild manifestations, with a striking predilection (about 95 per cent) for males.

Whether or not gout is clinically expressed, and if so in what degree, evidently does not depend upon the genetic endowment alone, since it is the predisposition to gout, not gout itself, which is inherited. The spectrum of expressivity, as pointed out elsewhere for inborn errors in general [17], is presumed to be the result of a complex interaction of genetic, metabolic and environmental influences involving the interplay of diet, endocrine functions, intercurrent diseases, the action of specific foods and drugs, emotional stresses, and other factors, all operating in the dimension of time. To illustrate the important role of the environment, particularly the diet, the overt manifestations of gout, common enough in England and on the Continent, virtually disappeared during the austerities of post-war life, only to return promptly in the same populations as the normal standards of living were resumed.

Natural History of Overt Primary (Classic) Gout. Although inborn, no sign or symptom of gout is detectable until hyperuricemia appears at about the age of puberty in males, later and in lesser degree in females. Hyperuricemia persists thereafter, with fluctuations in degree. The asymptomatic course of the metabolic abnormality proceeds unruffled until rudely interrupted by the onset of acute gouty arthritis, usually in middle age in males, even later in that much smaller proportion of female carriers in whom manifest disease develops. A succession of such self-limited attacks of acute gouty arthritis usually follows, at sporadic intervals, unaccompanied by consistent changes in serum or urine urate levels. The attacks may follow minor trauma to the affected joint, dietary indiscretions, the onset of intercurrent diseases, emotional upsets, and the like, but often no precipitating stress is recognizable. The joints involved are almost invariably those of the periphery of the extremities, classically the great toe. There may be renal colic and discharge of urate gravel or stone, to which gouty subjects are more prone than the population at large; indeed, renal colic due to urate stone occasionally is the first clinical manifestation of gout.

The intervals between attacks are free at first of joint symptoms. With time, however, there is

a gradual, insidious trend to further expansion of the urate pool. Tophaceous deposits form, with persistent joint involvement. Particularly vulnerable in tophaceous gout are the articular structures of the feet, ankles, knees, hands, wrists and elbows, and adjacent tendinous and subcutaneous tissues (chronic gouty arthritis); the cartilaginous pinna; the olecranon and patellar bursas (chronic gouty bursitis); and the kidney, the chief excretory organ for urate (gouty kidney). Only in the minority of cases, however, does deposition of urate occur at a rate rapid enough to produce marked injury. Despite such deformity and disability as may accrue, gout does not ordinarily seem to shorten life, and when death occurs it is usually through some interpolated cardiovascular, cerebral or neoplastic disease unrelated to gout but appropriate to the age and circumstances.

Analogies Between the Natural History of Gout and Those of Other Inborn Errors of Metabolism. Contrary to expectation, most inborn errors of metabolism are not apparent at birth but only after days or weeks (alkaptonuria [18], galactosemia [19], months (glycogen storage diseases [20]) or, as in the case of gout, even years; for example, the abiotrophy of Huntington's chorea, which usually gives no indication of its presence until age thirty to forty or even later. The similarities in this connection between essential hypercholesterolemia and gout are particularly illuminating. The serum cholesterol level in males normally remains static throughout the years of growth but increases markedly between the ages of about nineteen and thirty-two, then tapers off; in females the serum cholesterol level remains essentially unchanged until about age thirty when a slower but progressive rise begins [21]. The metabolic expression of genetically transmitted hypercholesterolemia in either sex ordinarily is delayed to well beyond childhood, the clinical expression as atherosclerotic coronary artery disease usually is not manifest until middle age in males and even later in females.

A distinct male predilection for overt disease, so long the subject of speculation in gout, is common to many other heritable disorders, viz. hemochromatosis [7], congenital "a"gamma-globulinemia [6], ankylosing spondylitis [22]. The genetic significance of more marked "penetrance" in one or the other sex without true sex-linkage is still obscure [14,23].

The acute attack of gouty arthritis, coming on as it does episodically in the steady course of the

underlying metabolic disorder, is reminiscent of the "crises" in other inborn errors of metabolism: the thrombotic crisis of sickle cell disease, the aplastic crisis of spherocytosis [17], the abdominal or neural crisis of intermittent acute porphyria [24], and the like. (Formerly, acute gouty arthritis was, in fact, referred to as a gouty crisis, a term which survives as "intercritical" gout, i.e., between crises). In sickle cell anemia, for example, the cycle of local hypoxia \rightarrow sickling \rightarrow increased blood viscosity \rightarrow intravascular clotting may be initiated by some determinate cause, such as exposure to high altitudes, but usually the sporadic occurrence of infarction cannot readily be explained. In porphyria many crises cannot be related to the known inciting agents (such as barbiturates), moreover there is no acceptable evidence that the acute attack is directly due to the excessive quantities of porphobilinogen or of its precursor, delta aminolevulinic acid, in the blood and urine; the pathogenesis remains unexplained [24]. Acute gouty arthritis likewise is of obscure origin, although popularly supposed to be brought about by the precipitation of uric acid in the tissues. There is much to suggest that uric acid, itself virtually inert physiologically, is not in fact the peccant matter involved [25-27]—that its sole "pathological vice . . . is its scanty solubility" [2]. Certainly hyperuricemia is neither a necessary nor a sufficient condition for development of the acute seizure, which fails to make an appearance in a variety of hyperuricemic diseases (nephritis with azotemia, many patients with blood dyscrasias, the asymptomatic hyperuricemia and intercritical phase of gout itself). Indeed, so dissociated is acute gouty arthritis from the gouty anomaly in purine metabolism reflected in hyperuricemia that the question of a genetic association rather than a causal relationship has been raised [28]. However, acute gouty arthritis occurs also in secondary gout, which is not genetically transferred.

The progressive deposition of urate in the tophaceous stage of gout conforms in every essential to the storage of lipids [10], carbohydrates [15,19,20], metals [7,29] or pigments [30] in various other inborn errors of metabolism. Positive imbalance in all such "storage" diseases is the result of the incapacity to metabolize or to excrete the substance in question at a rate sufficient to cope with the rate of biosynthesis or absorption from the gut, consequently there is accumulation in the tissues. Little or no degrada-

tion of urate being possible in man, apart from that accomplished by the bacterial flora of the gut, tophaceous deposits in gout may appear in the face of enhanced excretion of urate by the kidneys and bowel, although more often when, with the ravages of age and disease, renal excretion falters [37]. Urate which cannot be disposed of by excretion, and is retained, is deposited selectively at certain tissue sites of predilection, just as in Wilson's disease, for example, the accumulation of copper in the brain is particularly pronounced in the basal ganglia and putamen, and in galactosemia the storage of galactose-1-phosphate in the eye centers in the lens. Why cartilage is a site of predilection in gout is a matter of speculation, as it is in ochronosis.

Because of the daily passage of large quantities of urate through the kidneys and urinary tract, this excretory route is especially vulnerable to the deposition of urate. In normal man taking a low purine, restricted protein diet, some 5 to 10 gm. of urate filter through the glomeruli every twenty-four hours, and an additional quantity appears to be secreted by the tubules; all but about 400 mg. of the total is then reabsorbed by the tubules [31,32]. In the gouty subject the magnitude of urate transit down the tubular lumen and transfer across the tubular cells is, on the average, 50 per cent greater, sometimes more than twice as large [37]. Deposition in the renal parenchyma is therefore not unexpected, although urate does not accumulate as rapidly or as markedly as, for example, cystine in cystinosis, with development of the Fanconi syndrome [33].

The danger of precipitation of uric acid, in view of its insolubility in acid medium, presumably is greatest in the concentrated, acidified urine of the lower reaches of the nephron, the kidney pelvis and the urinary bladder; and, as has long been known, uric acid stone is a not infrequent complication of gout, occurring in 10 to 20 per cent of cases in temperate climates. The contributory factors are precisely those operating in normal subjects and in other inborn metabolic errors predisposed to stone formed of one or another sparingly soluble compound. These factors include an increased concentration in the urine, an unpropitious urine pH, and an infection of the urinary tract with or without stasis. A plethora of urate may appear in the urine in a variety of circumstances. Presumably as a result of especially augmented biosynthesis,

about 30 per cent of gouty subjects habitually excrete abnormally large amounts of urate in the urine (hyperexcretors), even on a diet restricted in purines and proteins [37]; in such cases the proportionate incidence of urate urolithiasis is substantially greater than in gouty "normal excretors." (Overproduction, with overflow into the urine and stone formation, occurs also, for example, in oxalosis [34]). Of course, the urinary excretion of urate is further enhanced, by several hundred mg./twenty-four hours, by dietary excesses in any gouty or non-gouty subject. In secondary gout overproduction of purines may be even more marked, and the incidence of urate stone in our experience, is 35 per cent [35]; indeed in hemopoietic and related disorders overproduction of urate may be so overwhelming in certain circumstances that both ureters may be plugged by crystals of uric acid. There does not seem to be an intrinsic deficiency in tubular reabsorption of urate in gout, analogous to that in cystinuria [36,37] for example, hence this is not a contributory factor except secondarily when there is diffuse tubular damage or when uricosuric drugs are employed. All too often these lead to urate stone formation if a large urine volume is not maintained. Even when uricosuric agents are not administered, reduction in urine volume and flow rate, due to inadequate water intake or excessive loss of water by routes other than renal, favors urate stone formation, as indicated by a 72 per cent incidence reported among gouty subjects in a torrid climate [38]. Excessive acidity of the urine (pH 4.5 to 5) often plays a predominant role in precocious and recurrent urate urolithiasis in the gouty as well as the non-gouty subject.

Urate Overproduction Versus Underexcretion in the Genesis of Hyperuricemia. More than a century of debate as to whether hyperuricemia in gout is due to overproduction or renal retention of urate is drawing to a close. It had been appreciated from the start [39] that simple retention of nitrogenous products, including uric acid, as in nephritis, does not of itself lead to the gouty state. But a weighty argument for a specific, intrinsic renal defect in excretion of urate has been the failure to account for excess of urate production in an increased urate output [39]. The validity of this point has been vitiated, however, by more recent detailed analysis which reveals that some 30 per cent of gouty subjects do in fact excrete urate excessively in the urine [37], and that the fecal excretion of urate amply makes

up for any apparent discrepancy between the rate of urate formation and the output in the urine [40].

If the hyperuricemia of gout were of renal origin, it could be brought about by reduced glomerular filtration, and/or excessive tubular reabsorption of urate, and/or reduced tubular secretion of urate. Renal clearance studies show, however, that the inulin clearance in gouty subjects usually is in a range commensurate with their age, and when reduced the reduction plainly is acquired [37]. As to reabsorption of urate by the renal tubules of the gouty subject, it is indeed greater than that of persons with normal serum urate levels but not measurably greater than when normal subjects are presented with comparably increased filtered urate loads [37]. The possibility of a specific, intrinsic deficiency in tubular secretion of urate has not been excluded, for want of suitable methods of study, but seems unlikely [37,32]; however, when the kidneys are aged or diseased, and demonstrably contribute to nitrogen (and urate) retention, impaired tubular secretion of urate may well be an accessory to the reduced glomerular filtration rate. It would appear, then, that the findings in gout are consonant with the experience in other inborn errors of metabolism, in which augmented blood levels are attributable, in general, to overproduction; deficient tubular secretion thus far has not been clearly shown to occur; and excessive tubular reabsorption has not been found. This last would imply genetic transmission of a *supranormal* enzyme complement for tubular transport.

Overproduction of urate must of necessity take place in gouty "hyperexcretors," in whom the basal excretion of urate in the urine alone (apart from fecal excretion of urate and nitrogenous products derived from urate) is greater than normal and hyperuricemia nevertheless is maintained [41]. In this group, moreover, isotope-labeled glycine is incorporated into urate in about three times the abundance found in normal subjects [42]. Such patients, however, constitute only a minority of patients with gout, as previously mentioned about 30 per cent. In the majority of cases, gouty "normal excretors," the urinary excretion of urate is within the limits of normal variation [37] and incorporation of isotope-labeled glycine into urate is not clearly augmented [42]. Excessive fecal excretion apparently occurs [40], however, implying overproduction of urate in these

patients also. Support for this implication derives from the increased turnover of urate reported under these circumstances [40].

Overproduction Due to Enzyme Lack in Inborn Errors of Metabolism. More data in direct corroboration of overproduction of urate in gout obviously are needed. Nevertheless it would not be profitless to pursue further in this direction the analogies between gout and other inborn errors of metabolism. Overproduction of metabolic intermediates is common enough in such disorders: for example, phenylpyruvate and its derivatives in phenylketonuria [43], homogentisic acid in alkaptonuria [44], a variety of aromatic amino acids in maple syrup urine disease [45], and many others. To be sure, these are all *intermediate* products of metabolic pathways whereas uric acid is essentially an *end product* of human tissue metabolism, a significant distinction but one which, as will be brought out subsequently, does not necessarily deny the operation of a metabolic block. The important point is that in every inborn error of metabolism characterized by overproduction this is not due to a surplus of enzyme in biosynthesis, but rather to a presumed or established genetically derived enzyme lack, in consequence of which a metabolic pathway cannot proceed to its ordinarily final step, and there is accumulation of metabolites formed before the site of the block. In phenylketonuria the missing enzyme has been identified as phenylalanine hydroxylase [43], in alkaptonuria as homogentisic acid oxidase [44], and so on. Thus far it has not been possible to pinpoint the enzyme(s) deficient in gout, but the "parsimony of Nature" suggests that a lack of specific enzyme(s) be sought as the key to the primary metabolic error(s) and hyperuricemia of this disorder.

Speculations Regarding the Nature of the Metabolic Error(s) of Gout. One enzyme lack to be considered in this connection is that of uricase, of which all mankind is bereft and thus the victim of a species-wide inborn error of metabolism. Loss of this enzyme, which seems to have disappeared in the course of mammalian evolution at some point before the branching off of the great apes, probably was not a mischievous mutation for our herbivorous forebears but it is a handicap to carnivores. It requires a nice adjustment of the means of disposal of uric acid to compensate for the loss of uricase but, even without the convenience of an avian cloaca, normal man accomplishes this with only an occasional lapse.

When to this injury, however, is added the insult of a metabolic error resulting in excessive formation of uric acid, the regulatory excretory mechanisms are subjected to even greater stress; if they are insufficient, urate retention and tophaceous deposits occur, on the other hand if renal excretion is too vigorous, urate may precipitate in the urinary tract. Gout clearly is not due to the lack of uricase *per se*, and there is every indication that the non-gouty and the gouty subject are equally deficient in this enzyme. In any event hyperuricemia, the only direct consequence of loss of uricase, does not constitute gout any more than hyperglycemia constitutes diabetes mellitus.

For the metabolic error(s) responsible for primary gout one should look, rather, to the long sequence of enzyme reactions effecting *de novo* purine biosynthesis from the precursors of uric acid [46]; the reactions by which these precursors are made available for purine biosynthesis; and to alternate pathways which compete with *de novo* purine biosynthesis for these precursors. From the general experience with other inborn errors, it may be inferred that the metabolic pathways affected in gout are already operative in normal man, and not novel shunts springing up, a *deus ex machina* as it were, from fresh mutations. It is to be anticipated further that, in the adjustments required to re-establish a steady state, the primary deficiencies in some pathways will be compensated for secondarily by the overactivity of others. Varying degrees of enzyme deficiency will in all likelihood be found, as in the heterozygotes of so many other inborn errors of metabolism [16]. What this means in precise genetic terms [47] is still uncertain but, the revelations of Ingram [48] and others [49] on the nature of the hemoglobinopathies suggest that minute variations in the DNA code [50] and in the corresponding amino acid sequences of the RNA-derived proteins may profoundly alter the properties of the active centers of enzymes.

It was formerly thought that uric acid originated solely or largely from preformed exogenous or endogenous nucleic acids, and that the hyperuricemia of classic gout was due entirely to exaggerated nucleic acid degradation, even though no sign of this is found in the tissues. It is now clear that the primary pathway of purine formation is *de novo* biosynthesis of purine nucleotides sequentially from simple units arising from glycine, glutamine, aspartic acid,

carbon dioxide, formyl derivatives of tetrahydrofolic acid and 5-phosphoribosylpyrophosphate (itself ultimately derived from dietary hexoses and phosphate) [46]. Conversion of the inosinic acid so put together to adenylic and guanylic acids then paves the way for polynucleotide formation by appropriate synthesizing enzymes [50], to provide the integral cellular RNA and DNA constituents required. The pool of nucleic acids elaborated at the end of this long cycle is expanded in the proliferative diseases underlying secondary gout, and turnover of this enlarged mass is presumed to be responsible for the hyperuricemia generated under these circumstances. The net turnover rate is relatively slow, being a reflection of the turnover of the cells containing the potential DNA and RNA sources of uric acid. There is a corresponding delay in the appearance of administered glycine- N^{15} in the urinary uric acid in secondary gout, peak isotope enrichment occurring on the tenth to fourteenth day [51]. In primary gout, peak isotope enrichment is much more rapid, occurring on the first to third day [52-54]. This prompt incorporation of glycine into uric acid is readily apparent in gouty hyperexcretors, in whom the peak is some threefold normal, but is also detectable in gouty normal excretors, despite the absence of discernible abnormality in total N^{15} incorporation, by an increase in the relative abundance of N^{15} in positions 1, 3, 9 on the first day [55]. The inference drawn is that the presumed overproduction of uric acid in primary gout springs chiefly from derangement(s) of some earlier step(s) in the sequences of purine biosynthesis, i.e., before the formation of intracellular DNA. There are many possible sites of such dislocation. Four general areas will be considered briefly here: (1) the sequence of reactions from 5-phosphoribosylpyrophosphate to inosinic acid formation; (2) the feedback mechanisms for control of purine biosynthesis; (3) the "salvage" pathways for reclamation of purine nucleotides from free purine bases and nucleosides; (4) the alternate pathways that compete with purine biosynthesis for precursors, in particular for glycine and other sources of amino acid nitrogen.

The results of isotope-labeling experiments [56-58] substantiate the thesis that *de novo* biosynthesis of uric acid involves the formation of inosinic acid as an obligate intermediate. Such being the case it is difficult to perceive how a block in the sequence of reactions from 5-phos-

phoribosylpyrophosphate to inosinic acid could result in other than *lessened* elaboration of uric acid, an end product of purine metabolism. (In respect to the site of metabolic block, then, the genesis of hyperuricemia in gout would appear to differ from the overproduction of metabolic intermediates in most inborn errors of metabolism). It would seem more logical to seek the enzyme lack(s) in gout in the metabolic events occurring before and/or after this chain of enzyme reactions.

It has been suggested [58,59] that an imbalance in the relative amounts of guanylic and adenylic acids generated for nucleic acid synthesis, with degradation of the excess nucleotide to uric acid, might contribute to overproduction of urate in gout, i.e., that there may be an enzyme defect in the feedback mechanisms which regulate this phase of nucleotide and nucleic acid biosynthesis [60]. Wyngaarden [61] has also called attention in this connection to another likely site for the feedback control of purine nucleotide biosynthesis, that implicit in the amidotransferase reaction of phosphoribosylpyrophosphate with glutamine to form phosphoribosylamine and glutamic acid.

There is also the possibility that deficiencies in specific pyrophosphorylases and nucleoside phosphorylases, which serve to salvage free purine bases and nucleosides of endogenous or exogenous origin by converting them to nucleotides, may result in excessive formation of uric acid. In the case of free purine bases, this involves competition for 5-phosphoribosylpyrophosphate with *de novo* purine biosynthesis and other metabolic pathways. The total urinary excretion of free purine bases in the urine of gouty and normal subjects is, however, essentially the same, about 50 mg./twenty-four hours [5,58,62,63].

Chronologically the oldest [52], and still perhaps the most attractive hypothesis, is that precursors of purine biosynthesis may be deflected from competing pathways, thus yielding an overabundance of urate, not because there is any intrinsic abnormality in the enzyme reactions leading to purine biosynthesis but simply because a surplus of building blocks is made available for elaboration of purines. This almost certainly occurs in secondary gout, by virtue of the aggressive demands of exaggerated hemopoiesis for nucleic acid precursors, just as in multiple myeloma amino acids may be diverted from serum albumin biosynthesis. In

primary gout overproduction of urate may take place by what might be termed "default of competing alternate pathways for utilization of precursors," for example, glycine and other sources of amino acid nitrogen and carbon. The concept implies that the enzyme lack(s) in primary gout may not reside in the sequential reactions of purine biosynthesis *per se*, but elsewhere. First suggested because of the excessive incorporation of total glycine-N¹⁵ into urate in some cases of primary gout, the hypothesis is supported by more recent evidence of differences in the intramolecular distribution of glycine-N¹⁵ in uric acid of gouty as compared to non-gouty subjects [64].

The experience with inborn errors of metabolism has disclosed again and again that what clinically may appear at first to be a nosologic entity is in fact a composite of disorders of distinct and sometimes quite disparate metabolic origin, with overlapping symptomatology. This applies, for example, to the glycogen storage diseases [20], the congenital methemoglobinemias [9], the congenital adrenal hyperplasias [65] and sporadic cretinism [66]. (The reverse also has occurred, as in the diverse clinical and biochemical abnormalities brought together by the finding of a common defect in erythrocyte glucose-6-phosphate dehydrogenase [67]). Such a multiple pathogenesis is already apparent in the primary and secondary forms of gout, which share a common clinical course to some extent and respond similarly to colchicine and uricosuric agents but derive from separate metabolic derangements [5]. One might, indeed, consider this subdivision to occur within the category of secondary gout, since the deoxyribo- and ribonucleic acids from which uric acid is formed in excess doubtless differ, depending upon their source in various hemopoietic disorders, each giving rise to what might be regarded as a particular metabolic variant of secondary gout. What clinically is called primary gout may very well prove ultimately to be a composite of metabolically distinct inborn errors [5,58]. There is in fact some suggestion of this inhomogeneity in the differences in glycine utilization for purine biosynthesis among gouty subjects [54,55]. Whether these are qualitative or quantitative is not yet clear, and further study will be required.

Concluding Remarks. It is appreciated that simply pointing out analogies between gout and other inborn errors of metabolism does not solve the problems of the pathogenesis of gout. And

yet these problems, considered in the broad context of other inborn errors, take on the outlines of a comprehensible even if not yet fully comprehended design, which lends itself to more purposefully directed further investigation. In any event, it is time to divest gout of the transcendental aura with which it has been enveloped since time immemorial.

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Clinical Studies

The Renal Excretion of Hydrogen Ion in Renal Tubular Acidosis*

I. Quantitative Assessment of the Response to Ammonium Chloride as an Acid Load

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DURING the past two decades numerous disturbances in particular functions of the renal tubule have been described. Many of these disturbances have been shown to be due to specific and genetically determined metabolic or enzymatic defects, and as such have contributed to the initiation of a new era of biochemical and molecular study of disease. Among these defects have been one or more of tubular transfer and excretion of hydrogen ions occurring in patients without the contracted kidneys and uremia of chronic progressive renal disease. The resultant syndrome generally has been called renal tubular acidosis. Such an acidosis was first described in children with diffuse nephrocalcinosis [1,2]; it has since been reported in a wide variety of clinical situations and in association with a series of other disturbances (some of genetic origin) in renal tubular function [3,4]. Because of this heterogeneous clinical setting there is great need for clarification of the pathogenesis and etiology of the specific defects involved in the renal excretion of acid. Furthermore, as indicated in a previous editorial [5], there are still many questions concerning the definition and the diagnostic differentiation of this type of renal acidosis.

In our own consideration of these questions we have studied a group of patients who appeared to fall into this category of renal acidosis associated with "non-contracted" kidneys and who

therefore were labelled clinically as having renal tubular acidosis (RTA). From comparison with normal subjects, we conclude that more than one mechanism is involved in the pathogenesis of the acidosis, and that minimal or subclinical degrees of the disturbance do exist. In arriving at this conclusion, we have found it necessary to establish more accurate criteria of the normal response to tests of the intrarenal processes of acid excretion. In this group of papers we report our attempt to do the following: (1) to assess quantitatively the ability of the kidney to excrete hydrogen ion under conditions of acid loading in normal subjects and in these patients diagnosed as RTA; (2) to assess the possible role of the enzyme carbonic anhydrase by the quantitative response to the administration of a standard single dose of the enzyme inhibitor, acetazolamide, in normal subjects and in patients with RTA [6]; and (3) to use the quantitative criteria of these tests in a search for latent subclinical defects in this tubular function in relatives of such patients [7].

The first of these three projects is reported in this paper. The administration of excess anion, usually as ammonium chloride, has been used by many workers [8-19] to test the ability of the kidney to excrete excess anion with hydrogen ion; this excretion protects and reconstitutes the buffering capacity of the body fluids. But, except for the short-term test of

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Wrong and Davies [18,19], the experimental conditions of such tests have not been sufficiently extensive or uniform to provide criteria that can be used on a quantitative basis. The study reported on herein is an effort to meet this need. To this end ammonium chloride was administered under comparable conditions to eighteen normal adult subjects and to five adult patients with clinical renal tubular acidosis. The renal response to this acid stress was analyzed in a variety of ways, both with respect to increment in excretion of hydrogen ion relative to increments in chloride loading or excretion, and with respect to absolute rates of excretion relative to extracellular buffer concentration. The former type of analysis, which has been the commonly accepted diagnostic procedure, is found in this study not to separate definitely these patients with RTA from the normal subjects. The latter type of analysis, which is analogous to a renal clearance of hydrogen ion, does separate these two groups and thus appears to provide a more adequate criterion for quantitative assessment of this aspect of renal function.

EXPERIMENTAL MATERIAL AND PROCEDURE

Twenty studies were conducted on control subjects (eighteen adult men and women apparently in good health and with no known disturbances in renal function). In two of these subjects the test was performed twice with the administration of different doses or loads of ammonium chloride. Five adult patients with the clinical diagnosis of renal tubular acidosis were tested, some of them more than once. The clinical diagnosis in three of the patients (A. B., M. B., M. C.) rested on the findings of metabolic acidosis in the absence of azotemia or ketosis, of relatively alkaline urines, and of nephrocalcinosis with or without nephrolithiasis. In the other two patients (H. L. and A. T.) the acidosis was intermittent and the urinary pH was not necessarily alkaline; to this extent these two patients did not meet the commonly held criteria for renal tubular acidosis. However, one patient (H. L.) exhibited extensive osteomalacia with pseudo-fractures and both patients (H. L. and A. T.) showed defective acid excretion during acid loading by Albright's test. Although in one patient (A. T.) episodes of acidosis and organic aciduria during paraldehyde ingestion subsequently developed [20], previously she had shown an extremely severe hyperchloremic acidosis without azotemia or ketonuria. For these reasons these patients have been included as examples of renal tubular acidosis, i.e., as having at one time or another acidosis due to failure of acid excretion by non-contracted kidneys with normal or only moderately impaired glomerular function. Three

of these patients have been reported on separately [20-22] but a résumé of each case appears in the Appendix. Certain data from one other patient (M.) have been included for purposes of comparison; this child who was observed by us and reported on in another paper [23] exhibited a cerebro-ocular-renal syndrome which included a renal acidosis due to a specific defect in ammonia production and excretion in a non-contracted kidney. Since he was not tested with ammonium chloride his full case report is not included herein.

The basic plan of the test was to administer orally ammonium chloride in a constant daily dose for three or five consecutive days and to collect a twenty-four-hour urine specimen on the first, third and fifth days, as well as during one to three preliminary control days. Samples of arterialized cutaneous and venous blood were taken during the control period and following the end of the third and the fifth days. The ammonium chloride was given in divided daily doses of a constant amount each day in each patient; the range of dosage among different subjects was 98 to 195 mEq. per 1.73 square meter of body surface area. Care was taken that blood specimens always were drawn at least seven hours after ingestion of the last portion of the daily dose. Uncoated tablets or aqueous solutions of ammonium chloride were used.

Two of the patients (A. T. and H. L.) and one normal subject (L. R.), were on a measured diet which provided a "neutral ash." The rest of the patients were maintained on their usual unmeasured diets during both control and test periods, being cautioned against taking any other medication. Some of the tests in the patients were limited to three days because of the degree of pre-existing acidosis.

CHEMICAL METHODS AND CALCULATIONS

Where different methods were used in the two laboratories, University of Cambridge and University of Pennsylvania, respectively, the references are given in that order.

In venous serum the total carbon dioxide content was determined by the manometric method of Van Slyke and Neill [24] and Van Slyke and Sendroy [25]; sodium and potassium were determined by flame photometry, chloride by the methods of Sendroy [26] and Franco and Klein [27], and creatinine by a modification of the methods described by Hawk, Oser and Summerson [28] and by the method of Bonsnes and Taussky [29]. In arterialized cutaneous blood the total carbon dioxide content and pH were obtained by the micromethod of Singer, Shohl and Bluemle [30], and the primary acid-base variables of buffer base concentration and CO₂ pressure derived from the nomogram of Singer and Hastings [37].

Normal acid-base values in one of our laboratories (University of Pennsylvania) are presented at the end of Table 1B.

In urine the pH was determined colorimetrically or

by a glass electrode, titratable acidity by titration with NaOH to pH 8.0 (University of Cambridge) or to 7.4 (University of Pennsylvania), * ammonium ion by the method of Folin and Bell [32]. Urinary chloride was measured by the Whitehorn-Volhard method as described by Cole [33] and by Harvey's modification of the Volhard method [34], sodium and potassium by flame photometry, creatinine by the method of Peters and Van Slyke [35], and sulfate by the method of Letonoff and Reinhold [36]. The urinary content of bicarbonate was calculated from the total carbon dioxide content and pH by the method of Peters and Van Slyke [37]. The twenty-four-hour urine specimens were collected and preserved under toluene and mineral oil in tightly capped refrigerated bottles.

Specific methods of calculation of each index of response to the ammonium chloride are presented in the analysis of the results. However, the basic calculation [38] of the renal excretion of hydrogen, UV_{H^+} , is taken as the sum of the excretion rate of titratable acid plus ammonium ion minus bicarbonate:†

$$UV_{H^+} = UV_{TA} + UV_{NH_4^+} - UV_{HCO_3^-} \quad (1)$$

For comparison of subjects and patients of different body size all values for UV_{H^+} and its component parts are corrected to a standard surface area of 1.73 M², calculated from height and weight by the method of Dubois. In every instance where excretion rates are expressed in equivalent units per minute, the values are those for twenty-four hours divided by 1,440 (minutes per day).

RESULTS

The results are presented in the following order: (1) the observed changes in blood and urine; (2) the derived relationships between increments in hydrogen ion excretion and in chloride loading or excretion (increment indices); and (3) the derived relationships of

* As calculated from the effect of pH on the total urinary excretion of acid phosphate in our subjects (University of Pennsylvania), this difference in titration point would result in about a 10 per cent difference in total hydrogen ion excretion between the subjects in the two groups on the third and fifth days of NH_4Cl ingestion. Such a positive "error" in the subjects (University of Cambridge) does not alter the relationships between the normal subjects and the patients with RTA as herein derived.

† This equation described the net acid-base effect of urine formation in the body; in terms of hydrogen ion balance the excretion of bicarbonate is a negative moiety since the loss of HCO_3^- in the urine leaves behind the associated H^+ of the $H \cdot HCO_3$ formed by hydration of metabolic carbon dioxide. In acid urines the HCO_3^- becomes a negligible fraction; hence in urines of pH 6.2 or less HCO_3^- was not measured. Therefore, in comparing the ratio $\Delta UV_{H^+} / \Delta UV_{Cl}$ with the data of other workers who have omitted the HCO_3^- moiety no significant error is introduced.

hydrogen ion excretion to extracellular buffer capacity as reflected by the plasma concentration of bicarbonate and total carbon dioxide.

Observed Data. Analyses of blood and serum (Table 1A) showed no evidence of metabolic acidosis in the normal subjects prior to ammonium chloride loading. As indicated by both the total carbon dioxide content of serum and the buffer base concentration in arterial whole blood (Table 1B), in all of the patients with RTA a metabolic acidosis was exhibited at least part of the time. During ammonium chloride loading a hyperchloremic acidosis developed or was exacerbated to varying degrees in each subject and patient tested.

The rates of excretion of chloride and of titratable acid and ammonium ion, and hence of hydrogen ion, increased relative to the control rates in each normal subject and patient during the administration of ammonium chloride and as shown in Tables 1A and 1B. As is well known, the increment in excretion of titratable acid in the normal subjects, and the decrement in urinary pH, occurred primarily during the first day; whereas the excretion of ammonium ion and, therefore, of total hydrogen continued, in the main, to be augmented. However, augmentation occurred at a decelerating rate during all five days of anion loading. (Fig. 1.)

The excretion rates of sodium and potassium rose on the third day and decreased again in most of the normal subjects on the fifth day of ammonium chloride loading. (Table 1IA.) The increment in excretion of these cations was less in the patients with RTA. (Table 1IB.) Phosphate excretion increased in all but one of the normal subjects and in two of the patients with RTA; in the other two patients with RTA (A. T. and H. L.) phosphate did not increase and the control rate of excretion was lower than in the other patients and subjects. Sulfate excretion remained relatively constant in those normal subjects in whom it was measured.

"Increment" Indices of Hydrogen Ion Excretion. Change in hydrogen ion excretion relative to change in the excretion of chloride has been employed in the past to measure the effectiveness of the renal response to administration of the excess chloride anion. Gamble, Blackfan and Hamilton [8] compared the increment in ammonium ion excretion with that in chloride excretion following a dose of calcium chloride; others [16,22] have used the ratio of increment in titratable acid plus ammonium ion excretion

TABLE I
AMMONIUM CHLORIDE LOADING TEST

Subject*		Day†	Urine‡					Venous Serum					Arterial Cutaneous Whole Blood								
			Volume (ml.)	pH	Titratable Acidity (mEq.)	Ammonium (mEq.)	Bicarbonate (mEq.)	Hydrogen § (mEq.)	Chloride (mEq.)	Creatinine (mg.)	Carbon Dioxide (mM/L.)	Chloride (mEq./L.)	Sodium (mEq./L.)	Potassium (mEq./L.)	Creatinine (mg. %)	Coll. vol. (%)	pH	Carbon Dioxide (mM/L.)	Buffer Base (mEq./L.)	Carbon Dioxide Tension (mm. Hg)	
M. S. 52.5, 173 1.50, 112	0 (2)	1290	6.1	20	25	45	129	1264	26.0	101	137	4.7	0.85
	3	1280	4.7	40	57	97	220	1196	21.0
	5	1090	4.6	37	75	112	171	1188	21.6	107	135	4.7	1.10
R. E. 77.9, 176 1.90, 150	0 (1)	2300	5.8	42	27	69	170	1760	26.5	107	144	5.0	1.20
	3	2020	4.5	65	71	136	204	1866	21.1	109
	5	1970	4.6	65	103	168	230	1793	21.4	111	141	4.7	1.25
E. C. 58.5, 170 1.66, 131	0 (2)	1725	6.2	29	20	49	158	1433	25.0	105	137	4.7	1.05
	3	3470	4.5	56	73	129	262	1370	...	109
	5	2965	4.6	54	103	157	335	1290	20.5	109	136	4.5	0.80
R. M. 50.5, 179 1.62, 112	0 (1)	1700	7.2	14	19	53	...	-20	394	1072	28.4	99	133	5.1	1.10
	3	2700	4.7	40	48	88	396	1120	24.7	102	134	5.2	0.90
	5	2940	4.9	35	49	84	488	1090	24.5	107	137	5.5	1.10
W. K. 76.0, 188 2.00, 150	0 (2)	1410	6.1	23	22	45	127	1631	...	99	141	4.4	1.15
	3	1760	4.6	58	84	142	235	1760	24.2	105	138	4.1	0.90
	5	2340	4.7	51	97	148	244	...	27.4	105	139	4.4	0.90
V. H. 56.1, 166 1.60, 124	0 (2)	1045	5.6	27	21	48	62	...	26.9	99	132	3.9
	3	2140	4.6	48	75	123	239	...	20.3	110	136	5.0
	5	1060	4.7	41	95	136	168	...	22.0	106	132	4.5
C. M. 54.1, 161 1.55, 137	0 (2)	827	5.9	22	25	47	79	...	25.8	107	137	4.7
	3	1575	4.7	42	76	118	287	...	17.2	109
	5	1650	4.7	39	112	151	272	...	16.2	...	136	4.3
E. H. 73.0, 184 1.83, 217	0 (1)	1005	5.97	29	36	65	163	...	25.7	105	44.1	7.40	19.4	46.0	37.0	...
	3	2385	5.00	59	159	218	413	...	17.6	111	49.5	7.31	13.5	39.5	31.5	...
	5	2100	5.12	54	220	274	406	...	17.8	112	45.9	7.32	13.6	39.0	30.7	...
L. R. 65.7, 185 1.85, 112	0 (3)	1277	6.44	19	40	5	...	54	109	1849	32.5	101	135	4.6	1.40	44.1	7.43	24.0	51.9	43.0	...
	3	1700	5.25	46	98	144	240	2040	26.0	104	141	4.0	1.10	46.3	7.41	21.6	49.4	40.5	...
	5	2360	5.30	44	107	151	231	2018	31.6	106	142	4.6	1.20	46.2	7.42	22.2	50.0	41.5	...
W. R. 84.0, 198 2.16, 128	0 (2)	1860	6.56	17	37	16	...	38	91	2271	26.1	107	139	4.1	1.13	47.3	7.37	23.0	49.0	47.0	...
	3	3020	5.20	48	99	147	365	2159	22.5	107	140	4.3	1.10	49.4	7.33	18.2	44.0	40.5	...
	5	1280	5.20	44	112	156	253	2220	21.3	110	140	4.0	1.10	49.4	7.33	18.8	45.0	42.5	...
L. B. 72.7, 185 1.92, 195	0 (3)	1322	5.66	38	40	80	164	1841	26.2	104	140	4.2	1.10	54.0	7.40	20.5	50.0	40.5	...
	3	3375	4.96	61	130	191	358	1850	18.4	110	141	4.3	1.10
	5	3610	5.20	60	157	217	343	1841	18.0	109	140	4.0	1.20	50.3	7.35	15.8	43.0	34.5	...

See footnotes on page 559.

TABLE I (Continued)
AMMONIUM CHLORIDE LOADING TEST

Subject*	Day†	Urine‡							Venous Serum						Arterial Cutaneous Whole Blood				
		Volume (ml.)	pH	Titrateable Acidity (mEq.)	Ammonium (mEq.)	Bicarbonate (mEq.)	Hydrogen § (mEq.)	Chloride (mEq.)	Creatinine (mg.)	Carbon Dioxide (mM/L.)	Chloride (mEq./L.)	Sodium (mEq./L.)	Potassium (mEq./L.)	Creatinine (mg. %)	Cell vol. (%)	pH	Carbon Dioxide (mM/L.)	Buffer Base (mEq./L.)	Carbon Dioxide Tension (mm. Hg.)
G. W. ¹	0 (3)	1480	6.00	36	49	...	85	145	2158	28.9	103	143	4.1	1.10	51.8	7.41	20.5	40.5	39.5
	3	2260	5.32	62	157	...	219	394	2192	24.9	107	142	4.5	1.14
	5	1620	5.40	62	180	...	242	310	2053	21.5	108	141	4.4	1.10	47.8	7.37	18.3	45.0	37.5
L. I.	0 (3)	846	6.59	13	25	6	33	162	1618	26.5	103	141	4.1	1.10	44.3	7.40	23.1	50.0	44.0
	3	1210	5.05	45	104	...	149	276	1694	16.7	110	141	4.0	1.14
	5	1165	5.47	49	197	...	246	288	1910	20.9	109	140	4.0	1.14	47.3	7.29	15.8	40.0	38.0
E. F.	0 (2)	1065	5.61	45	38	...	83	147	1986	26.7	105	141	4.5	1.35	45.2	7.43	21.0	49.0	38.0
	3	1880	5.00	70	104	...	174	323	2030	22.0	108	141	4.9	1.32
	5	1370	5.18	67	137	...	204	258	2192	21.6	110	141	4.7	1.28	47.8	7.29	17.6	42.0	42.5
R. J.	0 (3)	1222	6.18	30	35	3	62	124	1864	25.2	105	142	4.0	1.15	48.3	7.40	20.0	48.0	38.5
	3	1920	5.30	61	148	...	209	291	1757	19.3	110	141	4.2	1.04
	5	1620	5.38	49	157	...	206	265	1758	20.9	112	145	4.2	1.15	50.4	7.34	18.7	44.5	41.0
E. W.	0 (3)	1010	6.10	28	33	1	60	199	1732	23.7	105	141	4.3	1.13	47.8	7.42	21.4	50.0	40.0
	3	1965	5.33	62	117	...	179	496	1842	18.2	111	141	4.3	1.05
	5	1225	5.60	43	150	...	193	249	1848	21.1	111	143	4.0	1.06	46.4	7.40	17.2	44.0	33.2
R. E. ²	0 (2)	1698	5.48	37	29	...	66	165	1824	26.2	107	142	4.1	1.10	46.6	7.42	21.1	40.0	39.5
	3	1340	4.76	50	60	...	110	243	1658	20.2	109	141	4.5	1.04	47.3	7.40	17.4	44.5	33.5
	5	1610	5.10	46	84	...	130	282	1642	22.8	110	144	4.2	1.05	45.6	7.40	18.4	44.5	35.2
G. W. ³	0 (2)	1638	6.00	44	54	...	98	160	2080	29.6	105	144	4.5	1.10	46.9	7.44	20.5	48.5	36.5
	3	2060	5.28	47	92	...	139	298	2043	23.6	107	143	4.7	1.10	48.9	7.43	19.1	47.8	35.0
	5	1760	5.38	52	107	...	159	284	2081	26.1	109	144	4.9	1.10	49.9	7.40	18.8	44.5	36.8
E. B.	0 (2)	755	5.72	23	28	...	51	124	1415	24.7	108	144	4.6	1.00	45.2	7.44	20.1	48.0	36.0
	3	1720	5.00	48	118	...	166	331	1419	19.7	112	143	4.5	1.00	47.3	7.37	14.0	41.5	29.0
	5	1120	5.60	36	146	...	182	259	1344	16.9	...	143	4.0	1.10	44.5	7.36	13.4	40.0	28.0
J. M.	0 (3)	590	5.74	20	24	...	44	79	1847	26.1	104	140	4.0	1.10	50.9	7.42	22.1	51.0	42.0
	3	2890	5.23	48	135	...	183	455	2312	15.7	113	140	4.8	1.10	55.1	7.32	13.1	41.0	30.5
	5	1260	5.65	38	220	...	258	319	1953	18.5	...	139	4.0	1.00	53.0	7.41	13.6	43.0	26.0

B. Analyses of Blood and Urine in Patients with Renal Tubular Acidosis

A. T.	0 (1)	1710	6.20	19	27	1	45	97	933	25.7	104	139	4.0	0.70	41.1	7.37	20.1	45.5	40.0
	3	1135	5.30	26	42	...	68	119	922	20.2	107	136	4.0	0.67	41.6	7.42	17.3	44.0	31.0
	5	1525	5.18	31	62	...	93	157	1041	18.5	112	0.78	40.0	7.43	17.1	43.9	30.1
H. L.	0 (3)	1552	5.70	16	24	...	40	73	636	24.8**	104	140	4.7	0.90	42.5	7.43	21.9	48.0	38.0
	3	1840	4.75	21	51	...	72	148	611
	5	2080	4.72	23	79	...	102	153	596	16.2	122	139	5.0	0.70	37.0	7.40	15.7	41.0	28.0

TABLE I (Continued)
AMMONIUM CHLORIDE LOADING TEST

Subject*	Day†	Urine‡						Venous Serum						Arterial Cutaneous Whole Blood					
		Volume (ml.)	pH	Titrateable Acidity (mEq.)	Ammonium (mEq.)	Bicarbonate (mEq.)	Hydrogen § (mEq.)	Chloride (mEq.)	Creatinine (mg.)	Carbon Dioxide (mM/L.)	Chloride (mEq./L.)	Sodium (mEq./L.)	Potassium (mEq./L.)	Creatinine (mg. %)	Cell vol. (%)	pH	Carbon Dioxide (mM/L.)	Buffer Base (mEq./L.)	Carbon Dioxide Tension (mm. Hg)
A. B. 1.60, 112	0 (2)	...	7.2	-14	60	...	46	14.1
	3	...	7.2	27	70	...	97	8.1
M. B.¶ 1.48, 187	0 (1)	1510	6.72	11	25	7	29	69	900	20.0	103	142	4.3	0.87	47.0	7.30	14.8	40.0	34.5
	3	2510	6.40	32	49	5	76	203	1024	21.0	111	139	4.9	...	50.0	7.29	15.1	40.0	37.0
M. C.¶ 1.59, 112	0 (1)	3575	6.90	9	22	8	23	159	1162	15.5	114	141	3.6	1.43	50.8	7.36	11.9	39.5	25.2
	3	3830	6.25	29	43	...	72	265	1206	11.0	...	140	3.6	...	50.1	7.24	9.9	34.0	26.5
Normal subjects**		Data††																	
mean		27.7																	
-2 standard deviations		22.5																	
mean +2 standard deviations		32.9																	
number		(142)													(19)				
															7.42 21.2 48.8 37.6				
															7.38 18.6 45.0 30.4				
															7.46 23.8 52.6 44.8				
															(19) (22) (19)				

NOTE: For the values of titrateable acidity and bicarbonate in patient (A. B.) we are indebted to Dr. Paul Fourman.

* Data under subjects initials indicate, respectively, the weight in kilograms, height in centimeters, surface area in M² and daily dose of ammonium chloride in mEq.

† "Day" indicates control periods with number of days given in parentheses; the third and fifth day the patient was given ammonium chloride.

‡ Urine data are expressed in units per twenty-four hours uncorrected for body size.

§ Total hydrogen ion excreted calculated as T. A. + NH₄ - HCO₃⁻ (see equation 1 in text).

|| Specimens of blood for analysis were drawn at the end of the day indicated.

¶ Weights of two patients (M. B. and M. C.) were, respectively, 48.2 and 56.3 kg.

** Venous serum carbon dioxide content = 20.2 mM/L. thirteen days prior to this determination.

†† These data as determined at the laboratory of the University of Pennsylvania include normal subjects in this table.

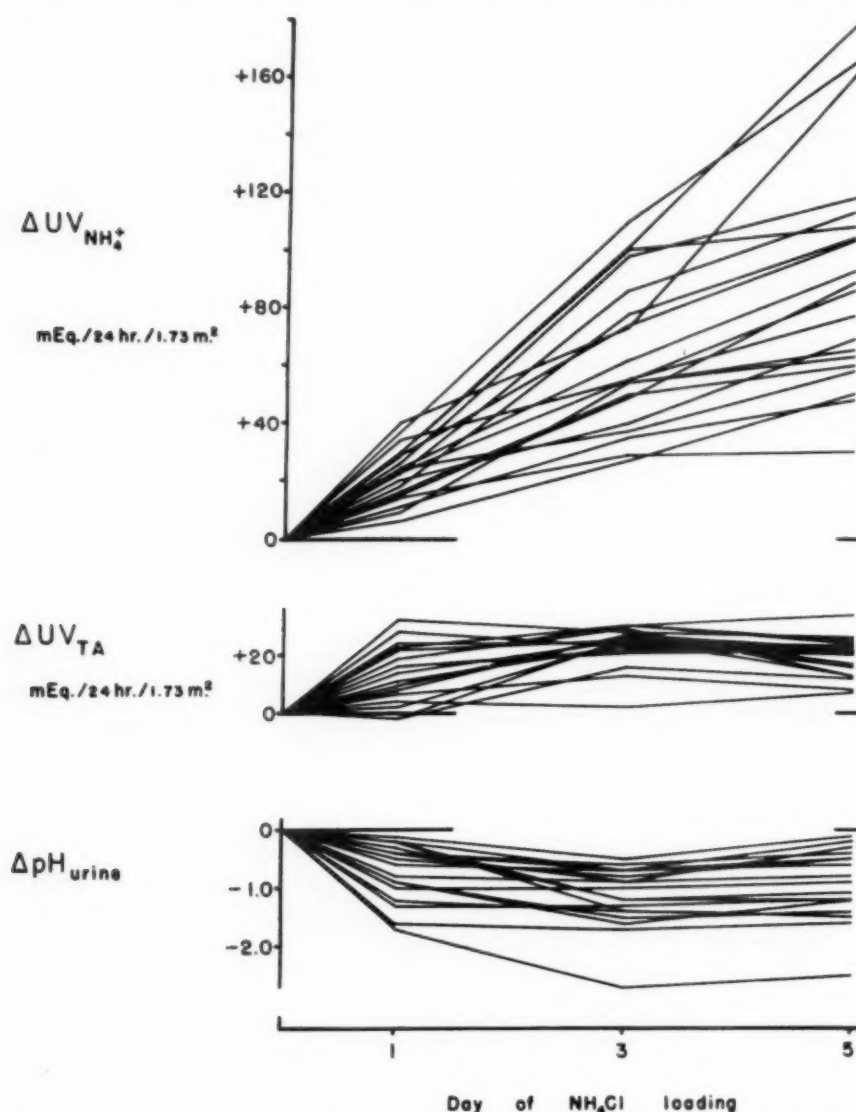


FIG. 1. Response of normal subjects to the administration of ammonium chloride for five days is shown: change from mean control values of the excretion of ammonium ion ($UV_{NH_4^+}$), the excretion of titratable acid (UV_{TA}), and urinary pH. Increase in excretion of titratable acid and decrease in urinary acidity occurred mainly during the first day and were maximal by the third day; the excretion of ammonium ion continued to be augmented in most of the subjects over the five days.

to that in chloride excretion to assess the adequacy of response to ammonium chloride ingestion. Calculation from our data of their index, as $\Delta UV_{H^+}/\Delta UV_{Cl}$, (see footnote † p. 556) indicates an almost complete overlap between the values for the normal subjects and those for our patients with RTA. (Table III and Fig. 2A.)

Change in hydrogen ion excretion relative to excess anion, or ammonium chloride, administered or "loaded," was the index used by Albright *et al.* [12] to demonstrate the defect in urinary acidification in their patients with "tubular insufficiency without glomerular insufficiency"; their control data, however, appear

to have been acquired from only one normal subject tested once. Our data for this index, $\Delta UV_{H^+}/\Delta Cl_{in}$, (where ΔCl_{in} equals the ammonium chloride given) indicate a considerable overlap between the normal subjects and the patients. (Table III and Figure 2B.)

Since it is apparent that neither of these "increment indices" definitively separates all the patients with overt renal tubular acidosis from all the normal subjects, these indices can hardly serve to identify latent cases of the disease. Yet, it is also obvious that the patient with a depressed concentration of total carbon dioxide and bicarbonate in his extracellular fluid but who in a

TABLE II
AMMONIUM CHLORIDE LOADING TEST*
Supplementary Data

Subject	Day*	Sodium (mEq.)	Potassium (mEq.)	Phosphate (mM)	Sulfate (mEq.)
<i>A, Normal Subjects</i>					
E. H.	0 (1)	162	72
	3	204	125
	5	143	114
L. R.	0 (3)	99	66	28	...
	3	131	99	37	...
	5	100	87	35	...
W. R.	0 (2)	105	73
	3	234	85
	5	122	87
L. B.	0 (3)	154	55	34	...
	3	190	115	44	...
	5	208	101	24	...
G. W. ₁	0 (3)	149	76	38	...
	3	198	136	46	...
L. I.	0 (3)	159	88	25	...
	3	156	94	31	...
	5	90	109	38
E. F.	0 (2)	147	63	36	49
	3	207	101	53	49
	5	103	111	48	49
R. J.	0 (3)	127	70	34	42
	3	178	72	47	53
	5	100	84	34	48
E. W.	0 (3)	202	62	31	40
	3	312	144	51	53
	5	105	79	36	61
R. E. ₂	0 (2)	161	70	29	39
	3	172	70	32	39
	5	181	89	37	49
G. W. ₂	0 (2)	151	97	50	61
	3	217	102	32	52
	5	200	88	37	61
E. B.	0 (2)	124	47	20	36
	3	179	98	36	37
	5	90	74	31	25
J. M.	0 (3)	79	40	18	32
	3	307	101	38	48
	5	107	81	16	53

TABLE II (Continued)
AMMONIUM CHLORIDE LOADING TEST*
Supplementary Data

Subject	Day*	Sodium (mEq.)	Potassium (mEq.)	Phosphate (mM)	Sulfate (mEq.)
<i>B, Renal Tubular Acidosis</i>					
A. T.	0	103	46	21	...
	3	75	53	19	...
	5	87	65	21	...
H. L.	0	72	37	14	...
	3	88	47	14	...
	5	70	51	15	...
M. B.	0	91	68	25	...
	3	130	132	41	...

M. C.	0	141	80	21	...
	3	172	130	33	...

NOTE: Urine data expressed in units per twenty-four hours uncorrected for body size.

* Day indicates control periods, with number of control days in parentheses, and third and fifth days when patients were given ammonium chloride.

steady state is excreting his usual daily dietary and metabolic "load" of hydrogen, is different from the normal subject with a normal concentration of carbon dioxide and bicarbonate; the patient has a lower "clearance" of hydrogen ion. Can the clearance of hydrogen ion be quantitated?

An Index of the Renal "Clearance" of Hydrogen Ion. The concentration gradient of free hydrogen ion between blood and urine can be measured and may reach the considerable magnitude of 1:800, but a clearance calculated in terms of dissociated hydrogen ion only is unsatisfactory for our purpose. Homeostatically, it is the undissociated but potentially ionizable hydrogen in the weak acids of the bicarbonate, phosphate and protein buffer systems that is regulated by the kidney. The concentration of these buffers is determined by the difference between "fixed" or "non-buffer" anions and total cations; in plasma in the absence of primary respiratory disturbances of acid-base balance the principal measure of this difference is the concentration of bicarbonate. But since in metabolic acid-base disturbances the content of undissociated hydrogen in the buffer systems rises when the bicarbonate concentration falls, and falls when

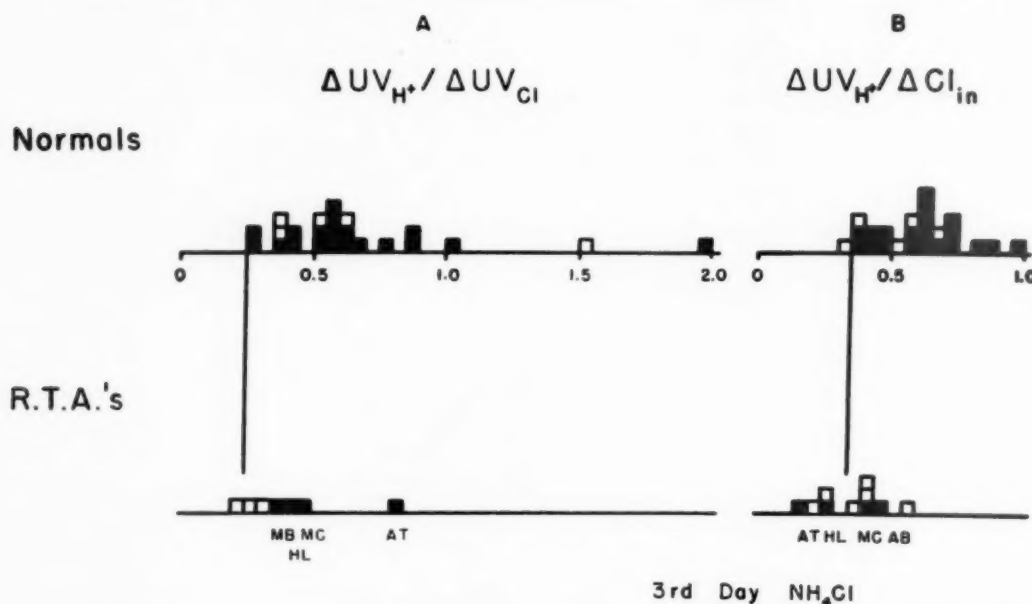


FIG. 2. Ratio of increment in hydrogen ion excretion to: (A) increment in excretion of chloride, and (B) increment in acid (ammonium chloride) load, in normal subjects and in patients with RTA. Black squares represent the data obtained in our own normal subjects and patients, open squares the data from the literature (Table v). Initials identify values for our patients with RTA. There is complete or partial overlap in distribution of the values of the two groups.

the latter rises, the plasma concentration of bicarbonate (or of total carbon dioxide) cannot be used as "P" in the basic clearance ratio, UV/P . For this reason we have used as P the reciprocal of the plasma or serum carbon dioxide content, $1/[CO_2]_p$, since this moiety rises and falls in proportion to the amount of buffered hydrogen ion in the extracellular fluid.* Although the use of units of measurement of different substances in the numerator and denominator prevents this value from representing a true renal clearance in the conventional sense, the resulting ratio is meaningful in that it is analogous to a renal clearance of total hydrogen ion and as such is empirically useful in the analysis of experimental data. If this reciprocal could be conceived of as P in units of concentration, then the term, UV/P , would express "ml." of plasma cleared per minute; but, since the reciprocal is not in itself a unit of concentration this "clearance" index is given simply as a numerical value, and is derived by multiplying

* In metabolic acidosis the total carbon dioxide content reflects primarily the concentration of bicarbonate. Use of the reciprocal of the bicarbonate concentration or of the buffer base concentration, as measured respectively in arterial plasma and whole blood [37], to calculate this clearance does not differ significantly from the results of the use of the serum content of total carbon dioxide, as proposed here.

the excretion rate of hydrogen, UV_{H^+} , in mEq. per minute per $1.73 M^2$ by the serum CO_2 content in mM per L.

The findings for this term are given in Table III; in the normal subjects the mean values and ranges on the third and fifth day, respectively, were 2.07 (1.4 to 3.4) and 2.47 (1.5 to 3.4). As shown in the distribution curves in Figures 3A and 3B, none of the patients with RTA overlap within the ranges of the normal subjects during acid loading, although prior to the ammonium chloride administration there was complete overlap. (Fig. 3C.) This clearance ratio or index, therefore, completely separates these patients with RTA from the normal subjects under the particular conditions of acid loading imposed for the test. With due allowance for this last qualification (which is discussed in detail subsequently), this index, $UV_{H^+}/1/[CO_2]_p$, is proposed as a definitive and sensitive criterion for the diagnosis of latent and minimal renal tubular acidosis.

Separate Assessment of the Excretion of Titratable Acid and Ammonium Ion. For consideration of the mechanisms of the renal excretion of hydrogen it is desirable to assess quantitatively the several moieties involved. Clearance indices for titratable acid and ammonium ion were calculated in the same way as for total hydrogen ion, i.e.,

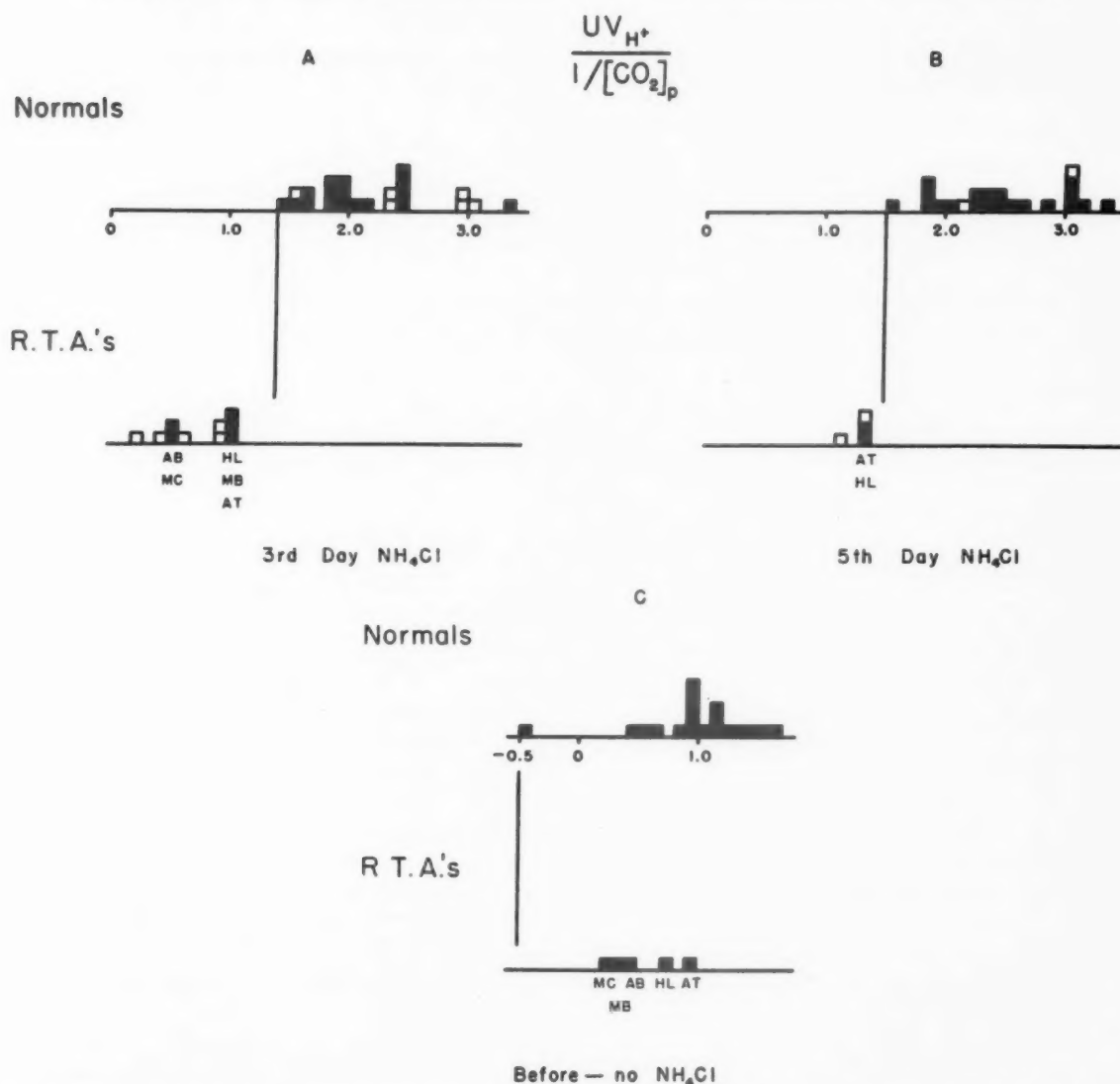


FIG. 3. Ratio of hydrogen ion excretion to the reciprocal of the plasma carbon dioxide (a clearance index) during ammonium chloride loading in normal subjects and in patients with renal tubular acidosis. (Symbols same as in Fig. 2.) A and B, there is complete separation of distribution of the values between the two groups on both the third and fifth days of ammonium chloride loading. On normal daily diets prior to acid loading this index does not separate the two groups, C; however, the values for the patients with RTA at this time are uniformly less than those of the normal subjects on the third day of acid loading.

their absolute excretion rates were related to the concomitant reciprocal of the serum total CO_2 content. The results are presented in Table III. In the patients with renal tubular acidosis under an acid load, the index derived from the excretion rate of titratable acid also is uniformly below the range of the same index in the normal subjects; the index from ammonium ion excretion is depressed to almost the same extent. An index of the relationship of these two fractions of hydrogen ion excretion to each other may be calculated as the percentage ratio of ammonium ion to the sum of titratable acid plus ammonium

ion excreted. (Table IV.) Values for this ratio in the patients with renal tubular acidosis on a given day of acid loading lay entirely within the range of those for all the normal adults. Both sets of data, at least, are evidence against a disproportionate impairment of the ability of the kidney to excrete ammonium ion in these five patients with RTA. In striking contrast, however, is the extremely low value for this ratio found in one patient (M.) who had a specific failure in the production of ammonia (reported on previously [23]).

Furthermore, as shown in Figure 4, of the

TABLE III
INDICES OF HYDROGEN ION EXCRETION DURING AMMONIUM CHLORIDE TEST

Group and Subject	Increment Indices (%)		Clearance Indices		
	$\frac{\Delta UV_{H^+} \times 100}{\Delta UV_{Cl}}$	$\frac{\Delta UV_{H^+} \times 100}{\Delta Cl_{in}}$	$\frac{UV_{H^+}}{1/[CO_2]_p}$	$\frac{UV_{TA}}{1/[CO_2]_p}$	$\frac{UV_{NH_4^+}}{1/[CO_2]_p}$
<i>Third Day of Ammonium Chloride</i>					
Normal adults					
n*	19	20	17	17	17
mean	66.2	61.8	2.07	0.75	1.32
maximum	197	97	3.4	1.0	2.4
minimum	29	37	1.4	0.6	0.8
Adults with renal tubular acidosis					
A. T.	82	20	1.1	0.4	0.7
H. L.	42	29	1.1	0.3	0.8
A. B.		46	0.6	0.2	0.4
M. B.	35		1.1	0.5	0.7
M. C.	46	44	0.6	0.2	0.4
<i>Fifth Day of Ammonium Chloride</i>					
Normal adults					
n*	20	20	20	20	20
mean	101.1	75.9	2.47	0.68	1.78
maximum	266	118	3.4	1.0	2.7
minimum	49	55	1.5	0.4	0.9
Adults with renal tubular acidosis					
A. T.	71	41	1.4	0.5	0.9
H. L.	76	55	1.4	0.3	1.1

* n indicates the number of subjects.

three patients with RTA with relatively high alkaline urines the excretion of ammonium ion relative to urinary pH was high in one (A. B.) and was near the upper limits of normal in the other two (M. B. and M. C.); in two other patients (A. T. and H. L.) excretion of ammonium ion lay within the relationship exhibited by the normal subjects. Again in contrast, the patient with the specific ammonia defect showed a very low excretion rate relative to urinary pH. But in the normal subjects and the rest of the patients the augmentation of ammonium excretion during acid loading is more than just a function of urinary pH and titratable acidity for it was clearly dissociated from the latter after the first day. (Fig. 1.) At least one other conditioning factor was the total acid load or dose which accounts for the spread among these ammonium excretion values on the third and fifth days; in this relationship the results in the patients with

RTA lay within or slightly below that of the normal subjects. (Fig. 5.) Thus the excretion of ammonium ion in the patients with RTA appears to be normal or high relative to that of titratable acid and to urinary pH, but is not elevated relative to the systemic acidosis and ammonium chloride acid load.

COMMENTS

The Use of these Quantitative Indices. The data presented indicate that the ammonium chloride loading test can be used for fairly precise quantitative assessment of the renal excretion of hydrogen ion in human subjects. Obviously such a test which requires care in its performance and lasts at least three days is not necessary in many cases of renal tubular acidosis. Patients with overt signs and symptoms of nephrocalcinosis or of osteomalacia can readily be

diagnosed on the basis of a diminished bicarbonate concentration in plasma, a low or normal arterial pH value, a relatively neutral or alkaline pH value in the urine, and the absence of azotemia, hyperphosphatemia, hyperglycemia, ketonemia and ketonuria. Three of our patients (A. B., M. B. and M. C.) belonged to this group; their urinary pH values were abnormally high in relation to the markedly depressed levels of carbon dioxide in venous serum. (Fig. 6.) On the other hand, in patients in whom there is minimal or intermittent depression of the serum bicarbonate level (as in patients H. L. and A. T.) such a test is necessary to bring out the physiological defect in ability to excrete acid. Indeed, even with three days of ammonium chloride loading the relationship of the serum carbon dioxide level to the urinary pH of these two patients did not differ significantly from that of the normal subjects. (Fig. 6.) In these two patients the abnormality in total acid excretion was established by relating the absolute rate of hydrogen ion excretion to the serum level of carbon dioxide. (Fig. 7 and Table III.) These observations underscore the fact that pH is a unit of intensity or concentration which indicates the gradient actively established in the kidney, but which gives no quantitative information as to the amount of acid or hydrogen ion being excreted per unit of time.

It must be apparent, therefore, that the chief usefulness of the type of quantitative assessment presented in this paper lies in its application to the diagnosis of borderline clinical cases or to the detection of latent defects of this renal function in subjects with no signs or symptoms of the disease. This latter application is illustrated in the third paper in this series in which an attempt to identify a genetically determined defect in the relatives of one of our patients is reported [7].

Conditions of the Test. Such detection of minimal abnormalities in the capacity of the kidney to excrete hydrogen ion requires careful consideration of the conditions governing the test procedure.

Duration of loading may be critical for detection of the minimal impairment. Wrong and Davies [18,19] have used the eight-hour response to a single ingested dose of ammonium chloride. This test is an excellent one for identifying patients with the specific defect in the ability of the kidney to acidify the urine; it is less likely to pick up minimal impairment of ammonium excretion because of the prolonged augmentation

TABLE IV
EXCRETION OF AMMONIUM ION AS PERCENTAGE OF
THE SUM OF TITRATABLE ACID PLUS AMMONIUM
ION EXCRETION

Group and Subject	$\frac{UV_{NH_4^+} \times 100}{UV_{TA} + UV_{NH_4^+}}$		
	No Ammonium Chloride (%)	Ammonium Chloride (Day 3) (%)	Ammonium Chloride (Day 5) (%)
Normal adults			
n*	20	20	20
mean	53.6	64.3	71.4
maximum	74	75	86
minimum	39	52	58
Adults with renal tubular acidosis			
A. T.	59	62	67
H. L.	59	71	78
M. B.	70	61	
M. C.	72	60	
A. B.		72	
M†	28		

* n indicates the number of subjects.

† Patient with specific defect in renal ammonia production, reported elsewhere [23].

over three to five days in the excretion rate of ammonium ion. Our normal subjects were tested on the first day of ammonium chloride loading; during this first twenty-four-hour period the excretion rate of titratable acid approached but did not always reach the maximum levels attained on the third day. (Fig. 1.) For this reason the third and fifth day were arbitrarily chosen by us for standard test periods.

Dosage of ammonium chloride, which ranged in these tests from 98 to 195 mEq./day/1.73 M², may not have to be held within narrow limits, the essential factor being the ingestion of a strongly acid diet. Dosage should be determined primarily by the condition of the subject being tested; the dose should be smaller in acidotic patients, and larger in subjects in whom a provocative test is being performed to bring out a latent minimal impairment. Timing of the divided daily dose is important. In several of our normal subjects one dose of ammonium chloride was taken in the early morning of the third day within one hour of the blood sampling. The serum carbon dioxide levels then obtained

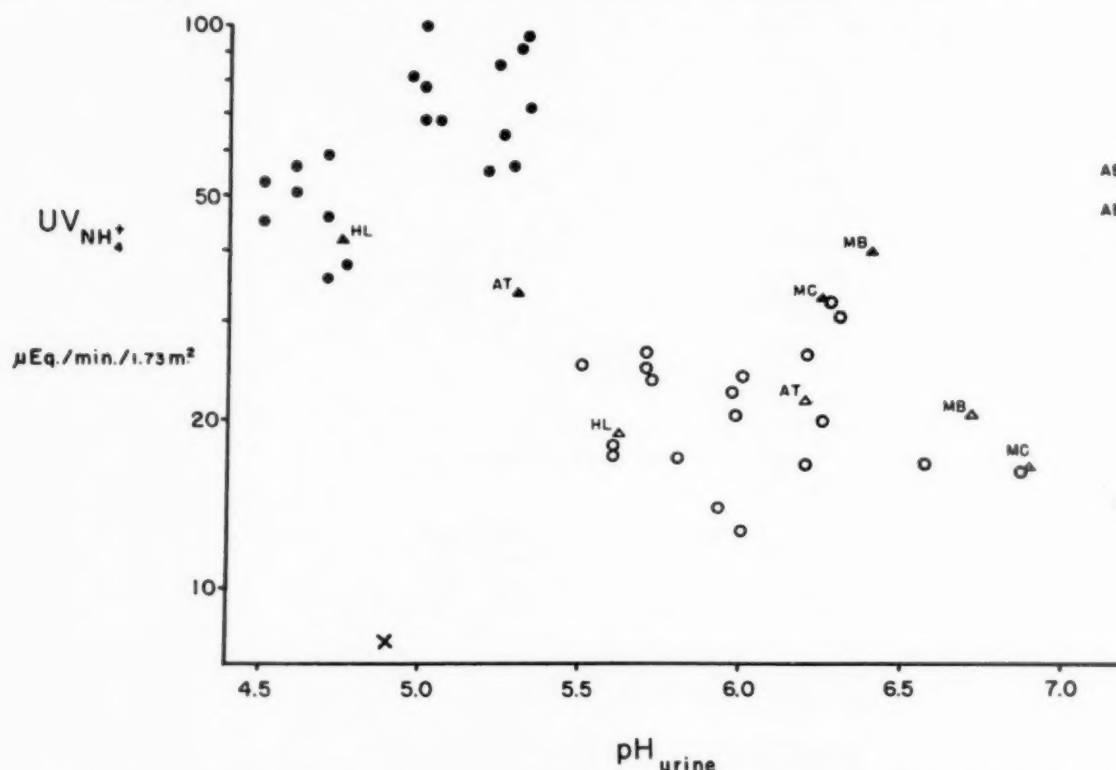


FIG. 4. Relation of the excretion rate of ammonium ion to the pH of the urine, in normal subjects and in patients with RTA. Round symbols represent normal subjects, triangles patients with RTA. Open symbols indicate control days prior to, and solid symbols third day of, ammonium chloride loading. The rate of excretion of ammonium ion varies inversely with the urinary pH in all normal subjects and in four of the five patients with RTA. However, three of the latter tend to have high rates of ammonium ion excretion relative to the pH of the urine. The cross represents the same relationship in a patient with renal acidosis due to a specific and primary defect in ammonium excretion (reported on elsewhere [23]); the patient was acidotic, but was not given ammonium chloride. In this case the excretion rate of ammonium ion is extremely low relative to the pH of the urine.

appeared to be unduly low and the data from these test periods were discarded. The last portion of the daily dose should be taken at least seven hours before the end of the twenty-four-hour period (usually at bedtime the night before).

For practical reasons, the daily diet was uncontrolled in most of our subjects who were asked to continue their normal dietary regimens and were warned against taking any acidifying or alkalinizing medication. Large variations in intake of neutral sodium chloride might affect the increment index based on changes in chloride excretion, $\Delta UV_{H^+}/\Delta UV_{Cl}$; in two normal subjects (C. M. and G. W.₂) with the lowest values for this index there was very little variation in the intake of sodium and/or chloride as reflected in the urinary output of these ions in the control periods. Hence this factor is unlikely to be the sole explanation of the overlap of values for this index between normal subjects and

patients with RTA. The other increment index in which change in acid excretion is related to ammonium chloride administered, $\Delta UV_{H^+}/\Delta Cl_{in}$, would be jeopardized by any large change in endogenous production of hydrogen ion or in the balance of fixed anions to fixed cations in the daily diet. Error due to variation in intake of chloride is rendered unlikely by the close correlation in the control periods of the daily excretion of sodium to that of chloride, whereas there was no correlation between the excretion rates of chloride and of hydrogen ion. The possibility of error due to variation in endogenous production of hydrogen ion has been assessed by examination of our data on the urinary excretion of inorganic sulfate in eight of our normal subjects. Insofar as the excretion of sulfate mirrors the metabolic production of hydrogen ion, these data suggest that variation in the latter factor between control and test periods does not account for the failure of the increment indices

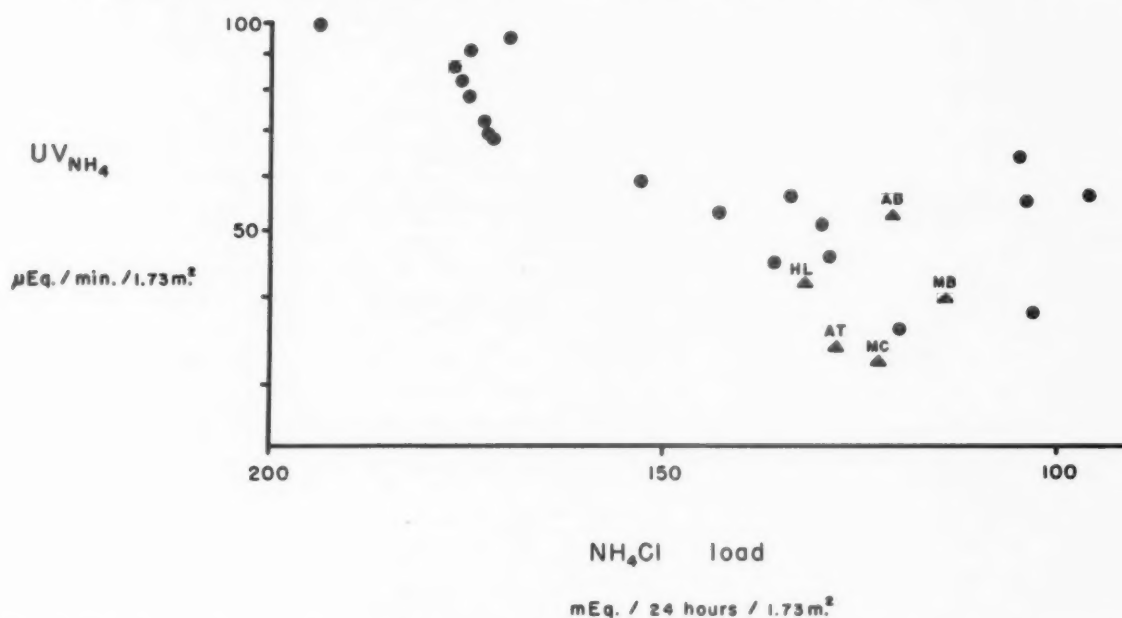


FIG. 5. Relation of the excretion rate of ammonium ion on the third day to the daily amount of ammonium chloride given, in normal subjects and in patients with renal tubular acidosis. (Symbols same as in Fig. 4.) The excretion rate of ammonium ion varied directly with the acid load.

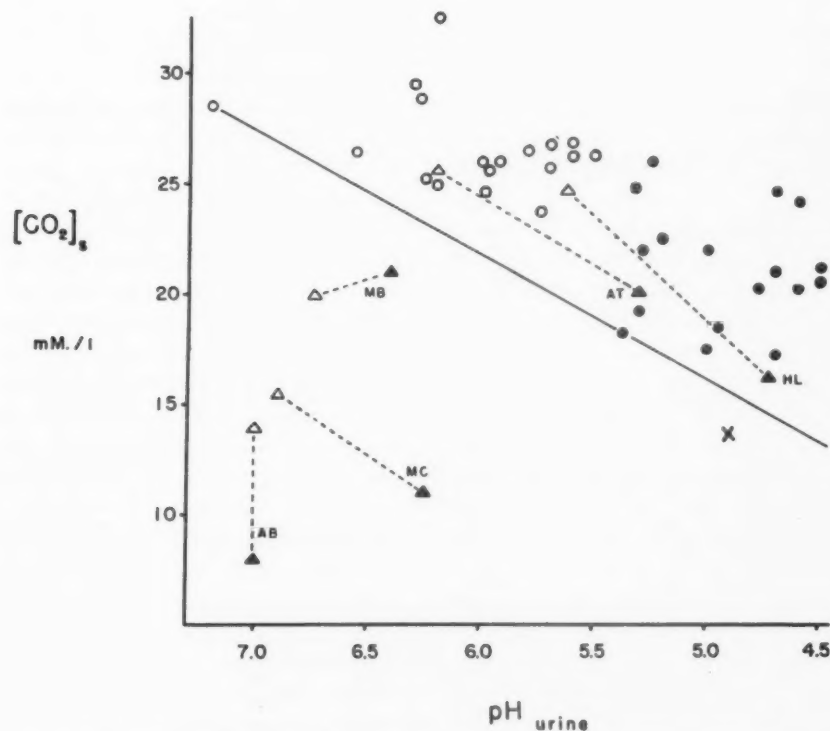


FIG. 6. The relation of the total serum content of carbon dioxide to urinary pH in normal subjects and in patients with RTA before and during ammonium chloride loading. (Symbols same as in Fig. 4.) Solid line roughly indicates the lower limit of this relationship in the normal subjects. The test in three of the patients with RTA clearly had abnormal results; the other two patients (A. T. and H. L.) and the patient with the ammonium excretion defect (x) were not differentiated from the normal subjects by this relationship.

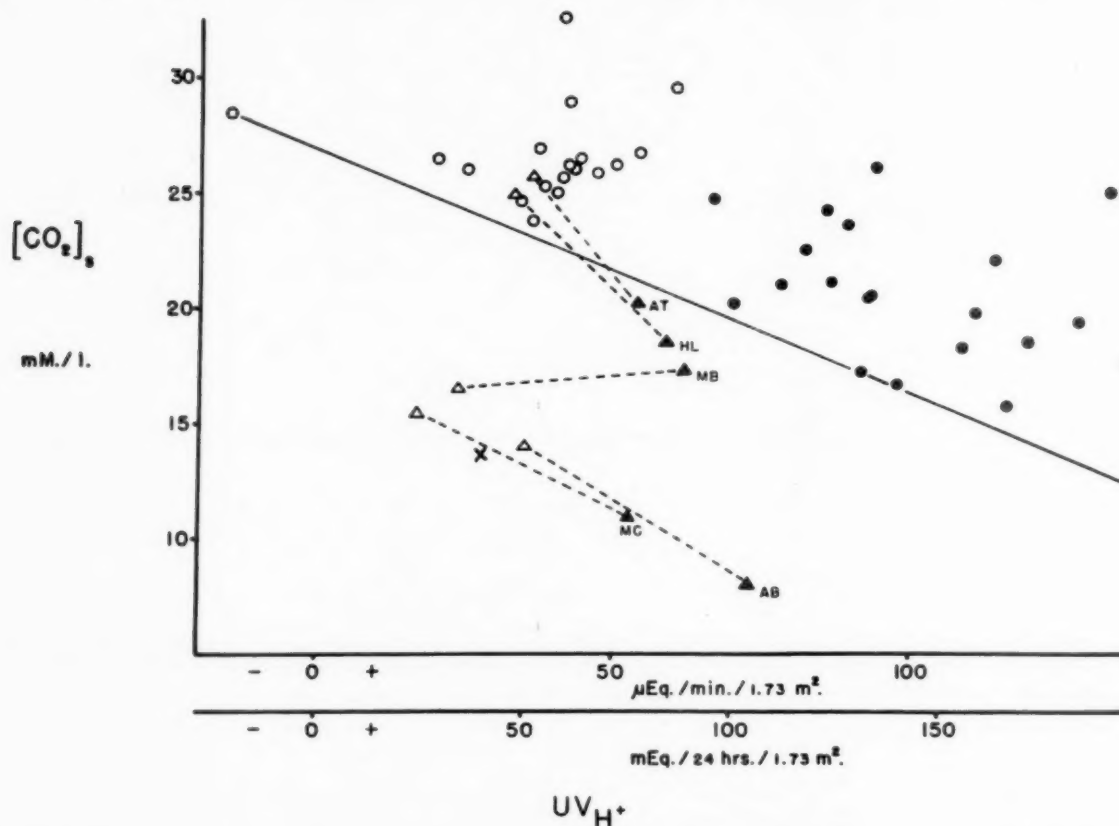


FIG. 7. The relation of the total serum content of carbon dioxide to the absolute rate of hydrogen ion excretion in normal subjects and in patients with RTA. (Symbols same as in Fig. 4.) All the patients are differentiated from the normal subjects by this relationship.

to separate the patients with RTA from the normal subjects.*

The necessity for acid loading requires some

* Other investigators have presented evidence that the major part of the metabolic production of hydrogen ion is due to the oxidation to sulfate of sulfur-containing amino acids and in a lesser degree to the incomplete metabolism of organic acids derived from fat and carbohydrate [39,40]. In seven of our normal subjects the daily excretion of sulfate in the control periods was equivalent, on the average, to 61 per cent of the daily total hydrogen ion excretion (range: 48 to 100 per cent). (Table II A.) The mean sulfate excretion rate for all the periods (control and acid loading) for each subject ranged between 31.5 and 50.4 mEq. per twenty-four hours per 1.73 M²; the standard deviations from these means averaged ± 6.3 (range ± 2.9 to ± 8.6) mEq. per twenty-four hours per 1.73 M². On the third day of ammonium chloride loading in each subject twice this standard deviation equalled but 2 to 7 per cent of the total excretion of hydrogen ion. Furthermore, in one subject (R. E.), whose increment index $\Delta UV_{H^+}/\Delta UV_{Cl_{in}}$ was the next to lowest value and overlapped the same index in some of the patients with RTA, the sulfate excretion rate on the third day of ammonium chloride loading was exactly the same as the average control rate.

consideration. In the use of the clearance indices proposed in this paper the total amount of acid given or of hydrogen ion presenting to the kidney does not need to be measured since the absolute rates of hydrogen ion excretion, and its moieties, are compared only with the level of extracellular buffer. However, the clearance indices only separate the normal subjects from the patients with RTA when the normal subjects are on a diet made acid by the addition of ammonium chloride. (Fig. 3.) Clearance indices of patients with obvious metabolic acidosis (who are carrying an extra exogenous load of acid) can be compared with indices of normal subjects given extra endogenous acid. But where the person being tested is in a questionable borderline state the critical comparison requires that the diet be strongly acid (i.e., that the subject be given ammonium chloride) in order to decide whether or not there is impairment of this renal function. Six grams (112 mEq.) of ammonium chloride added daily to the average acid-producing diet of an average-sized adult probably will insure an

adequate load of acid; higher doses are required in subjects whose normal diets are more alkaline.

The Nature of the "Clearance" Calculations for Hydrogen Ion. Although the rationale of such a calculation has already been presented, the nature of these clearance calculations requires some further comment. The buffer capacity of the body fluids, and more especially of the extracellular fluid, is equal to the difference between the fixed or non-buffer cations and anions or to the sum of the buffer anions. Singer and Hastings [37] have shown that this moiety, called by them "buffer base," may be quantitated in red cells and plasma. Determination of changes in the concentration or amount of buffer base in a fluid phase is the most direct way to measure a change in the buffer capacity or potential hydrogen ion content of that phase; the actual hydrogen ion concentration or pH is but an indication of the proportionality between the acidic and basic components of the buffer systems. Respiratory activity regulates extracellular pH by affecting this proportionality through changes in the level of one of the principal weak acids, carbonic acid. On the other hand, the regulatory activity of the kidney consists of the maintenance or restoration of the buffer capacity, or buffer base, of the body fluids. Although the tubular reabsorption of bicarbonate appears to be a function of the pressure of carbon dioxide (P_{CO_2}), the excretion of bicarbonate and hydrogen is a function of pH [38]. In metabolic acidosis, in which the filtered load of bicarbonate is drastically reduced, no bicarbonate is excreted, although the total reabsorption of bicarbonate diminishes along with the compensatory lowering of P_{CO_2} . (Table 1A and 1B.) But, the excretion of hydrogen ion is increased and correlates directly with the reduction in buffer base and bicarbonate (and increased hydrogen content of the buffers) in extracellular fluid, and perhaps in the renal tubular cells as well.

Under the ordinary circumstances of an acid-ash diet, the kidney performs its acid-base regulation by excreting the "surplus" fixed anions with hydrogen ions and with ammonia and by conserving buffer base mainly in the form of bicarbonate. Theoretically the most precise measurement of this renal function would be in terms of the excretion rate and clearance of buffer base. In the metabolic circumstances requiring the excretion of hydrogen ion, the

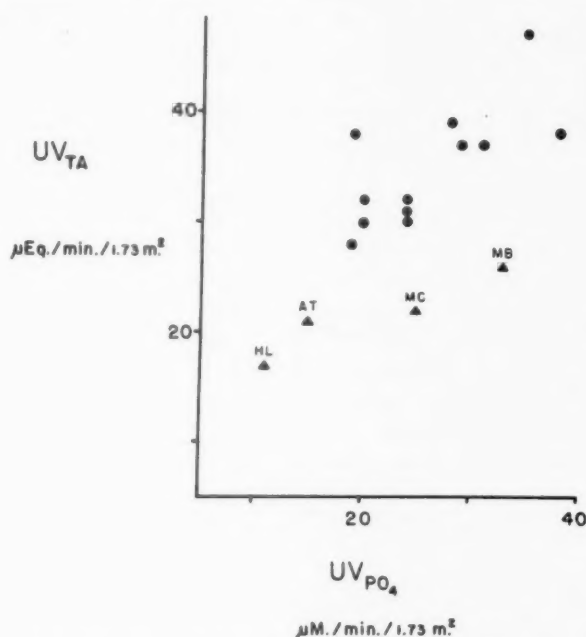


FIG. 8. The relation of the excretion rate of titratable acid to that of total phosphate during the third day of ammonium chloride loading, in normal subjects and in patients with RTA. (Symbols same as in Fig. 4.) The excretion rate of titratable acid was lower in all the patients with RTA than in the normal subjects. In two of the patients with RTA (H. L. and A. T.), however, this was due to a lower rate of excretion of phosphate rather than to a lesser degree of acidification of the phosphate buffer present in the urine, as in two other patients (M. C. and M. B.).

excretion rate of buffer base is a negative quantity; this is also true of the clearance calculated by dividing the excretion rate of buffer base by the concentration of buffer base in blood. In each of our normal subjects and patients in whom this latter concentration was measured, the clearance of buffer base was calculated and was found to become more negative as the hydrogen ion intake or load was increased.* The differences between the normal subjects and patients with RTA were essentially the same as the differences between the two groups of the more simply calculated indices of hydrogen ion clearance based on the rate of excretion of total hydrogen and the reciprocal of the serum content

* The range of clearance of buffer base, $UV_{BB}/[BB]_b$, in five normal subjects on the third day of ammonium chloride loading was -1.2 to -2.2 ml. per minute per $1.73 M^2$; these values in three patients with RTA (A. T., M. B. and M. C.) were, respectively, -1.0 , -0.9 , and -1.0 ml. per minute per $1.73 M^2$. Urinary buffer base, UV_{BB} , was calculated according to the method suggested by Barker and Singer [52] as: $(UV_{HCO_3^-} + 0.8 UV_{PO_4} \text{ in } \mu M. \text{ per minute}) - (UV_{TA} + UV_{NH_4})$.

TABLE V
INDICES OF HYDROGEN ION EXCRETION
Data from the Literature

Investigators and Subject	Increment Indices (%)		Clearance Index
	$\frac{\Delta UV_{H^+} \times 100}{\Delta UV_{Cl}}$	$\frac{\Delta UV_{H^+} \times 100}{\Delta Cl_{in}}$	$\frac{UV_{H^+}}{1/[CO_2]_p}$
<i>Third Day of Ammonium Chloride</i>			
Normal adults			
Linder ([9] II*)	38	60	2.4
Linder ([9] III*)	38	38	2.4
Gordon et al. ([13] D. H.)	61	55	3.0
Gordon et al. ([13] D. F.)	53	34	2.9
Gordon et al. ([13] D. S.)	155	68	3.0
Reynolds ([47] ave. 13†)	...	70	1.6
Renal tubular acidosis			
Linder et al. ([42] H. M.)	32	38	0.9
Smith and Schreiner ([43] No. 2*)	...	<56	0.7
Sirota and Hamerman ([44] A. B.)	<30	<43	0.3
Reynolds ([47] J. D. *)	...	42	0.0
Reynolds ([47] D. H. *)	...	24	1.5
Frick et al. ([45] Pt. *)	22	27	0.8‡
<i>Fifth Day of Ammonium Chloride</i>			
Normal adults			
Albright et al. ([12] L. C. *)	...	90	3.1
Sartorius et al. ([14] P.)	95	108	2.2
Renal tubular acidosis			
Albright et al. ([12] M. St. P.)	...	59	1.2
Jackson, Linder ([3] Jan.)	65	45	1.4

* Surface area assumed, from weight when given.

† Average for thirteen normal subjects, average surface area assumed to equal 1.73 M²; these data were published after our study was completed.

‡ Calculated on the assumption that the serum carbon dioxide content was the same in the third as on the fourth day of administration of ammonium chloride.

of total carbon dioxide. Hence we have adhered to the latter for our investigative purposes.

Application of These Calculations to Data in the Literature. Although much has been written about the urinary excretion of acid in normal subjects and in patients with renal tubular acidosis, there are relatively little data that can be submitted to our analysis. This is due to a variety of difficulties; urinary analyses were incomplete, serum analyses were not made or did not correspond to our arbitrary timing, no control periods were obtained, or the acid load was varied from day to day. For those normal subjects and patients whose data have been

submitted to our analysis, the results are presented in Table v as well as in Figures 2 and 3 [3,9,12-14,41-45]. There is good agreement with our own results in both normal subjects and patients with renal tubular acidosis. This is especially reassuring in the case of the three normal newborn infants studied by Gordon, McNamara and Benjamin [13] for some of our subjects to be reported on subsequently [7] were children. However, more normal data are urgently needed in the younger age groups.

Evidence Concerning the Pathogenesis and Types of Renal Tubular Acidosis. This problem will be discussed in detail elsewhere [6], but the data

presented here shed some light on the renal mechanism involved. Hydrogen ion excretion did not seem to be limited primarily by impairment of the production of ammonia and its excretion as ammonium ion. As other workers have found [18,19,45,46], the excretion rate of ammonium ion tended to be high in relation to the pH of the urine in some of these patients (Fig. 4); this suggests that limitation of ammonium ion excretion is not primary but is a secondary effect of the abnormally high pH of the tubular urine. In all five of our patients the excretion of ammonium ion relative to the degree of systemic acidosis, i.e., the clearance index, was depressed but the depression was not out of proportion to that for titratable acid. Thus the availability of ammonia as a proton acceptor does not appear to be the primary limiting factor, as apparently it is in generalized renal disease such as chronic glomerulonephritis [18,19,47,48].

The abnormality in these patients, therefore, is to be looked for in those renal processes that are involved in the reabsorption of bicarbonate, the excretion of titratable acid, and the establishment of a high gradient for hydrogen ion between blood and urine. Three of our five so-called patients with "RTA" clearly had an inability to establish this gradient; the other two (A. T. and H. L.) were able to maintain a normal hydrogen ion gradient, as shown by an acid urine (Fig. 6), but excreted total amounts of titratable acid and of total hydrogen ion that were low relative to the systemic acidosis as indicated by the serum carbon dioxide level (Fig. 7.) One limitation in these patients was the amount of urinary phosphate buffer available to accept hydrogen ions. As shown in Figure 8 and in Table II, the rate of phosphate excreted by these two patients was not only lower but, in contrast to two of the other patients with RTA and to all but one of the normal subjects, did not increase on acid (NH_4Cl) loading; factors controlling the availability of phosphate, other than glomerular filtration, must have played a role in these two patients. Such factors might well include inadequate intake of phosphate, defective intestinal absorption of phosphate (as in resistance to vitamin D or steatorrhea), or decreased parathyroid activity, all of which would cause increased tubular reabsorption and hence decreased excretion of phosphate acceptors of hydrogen ion. Experiments in severely acidotic dogs in our own laboratory [49] have indicated that in the presence of unlimited amounts of

phosphate in tubular urine a ceiling on the tubular transfer of hydrogen ion is reached that is some ten to twenty times the maximal rate occurring in the absence of extra phosphate. None of our patients were infused with phosphate but other investigators have shown that in some patients with RTA [41,43-45,50] as well as in normal subjects [51] this procedure leads to an increase in the total amount of titratable acid excreted although not to an increase in hydrogen ion gradient. These observations make it unlikely that the limiting factor is solely the ability of the tubules to donate protons against a low hydrogen ion gradient. Other factors that must be involved are the primary impairment of tubular proton donation against a high gradient (failure of the hydrogen ion pump), or primary lack of phosphate proton acceptor for causes other than depression of glomerular filtration. In addition, primary lack of ammonia as a proton acceptor has been documented by our group in another case of renal acidosis in a patient with a non-contracted kidney [23]; data from this patient are shown in Table IV and in Figures 4, 6 and 7 for comparison. Thus, patients without contracted kidneys may excrete inadequate amounts of hydrogen ion due to causes other than failure of the "hydrogen pump." Whether or not they should be labelled renal tubular acidosis is a matter of definition. Perhaps some new diagnostic classifications of renal acidosis are needed.

In any case, factors of tubular donation of protons need to be examined in these patients. Since the enzyme, carbonic anhydrase, plays an important role in facilitating the renal tubular processes of ion exchange and bicarbonate reabsorption it has seemed reasonable to assess the function of the enzyme in this disease. By use of the inhibitor, acetazolamide, we have made an attempt to study this problem in some of the same patients herein reported on; this study is presented in the second paper in this series [6].

SUMMARY

In order to establish criteria for the quantitative assessment of the renal excretion of hydrogen ion in patients suspected of having renal tubular acidosis, or in their relatives who might have a genetically determined latent impairment of this function, a standard three day and five day ammonium chloride test was performed twenty times in eighteen normal adults. The results were analyzed and compared with similar data from

five adult patients with the clinical diagnosis of renal tubular acidosis. The results show that:

1. Increment indices, in which the change in hydrogen ion excretion is compared with the increment in chloride excretion or in acid load, do not always separate the patients from the normal subjects.

2. A clearance index in which the absolute excretion rate of hydrogen ion is related to the total hydrogen content of the extracellular buffer systems (quantitated as the reciprocal of the serum carbon dioxide level) does separate the patients from the normal subjects under circumstances of an increased total hydrogen load.

3. In these adult patients with renal tubular acidosis the primary impairment of hydrogen ion excretion appears to involve the excretion of titratable acid; the excretion of ammonium ion is somewhat less deficient relative to the degree of systemic acidosis and normal or high relative to the pH of the urine.

4. Two of the patients with RTA were primarily limited in their ability to excrete acid by the amount of phosphate available in the tubular urine to accept hydrogen ions, and the other three patients with RTA were primarily limited by the capacity of the tubular cells to reabsorb bicarbonate and to transfer hydrogen ions against a concentration gradient. Thus more than one mechanism of acid excretion apparently is disturbed in renal tubular acidosis if all patients are included who have actual or potential acidosis due to "non-contractive" disease of the kidney.

It is concluded that the test and data here presented provide a tool for the investigation of the pathogenesis and etiology of latent as well as overt disturbances in this renal function.

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analytical work we are indebted to the members of the technical staffs of the Department of Experimental Medicine in Cambridge and of the Chemical Section of the Department of Medicine at the University of Pennsylvania.

APPENDIX

Brief summaries of patients with clinical renal tubular acidosis are presented:

CASE I. A. T., a thirty-seven year old white housewife of Italian descent, was first seen in February 1950 in the Hospital of the University of Pennsylvania. She was admitted unconscious, hyperventilating, and in a state of extreme metabolic acidosis. Results of laboratory data were as follows: arterial pH 6.97; venous serum carbon dioxide 4 mM/L.; chloride 126, potassium 2.6, and sodium 136 mEq./L.; calcium 12, phosphorus 1.9, and blood urea nitrogen 15 mg. per cent; urine showed a pH of approximately 5. The patient was treated with potassium, sodium and calcium alkali salts; one month later the results of an ammonium chloride loading test appeared to confirm the diagnosis of tubular insufficiency without glomerular insufficiency. There was no roentgenographic evidence of osteomalacia or nephrocalcinosis and the urogram showed normal appearing kidneys. On this first admission the patient had no abnormal degree of organic aciduria.

The patient has been followed up for eight years and her health has improved. She received alkali salts daily for the first two years. There was a second episode of severe acidosis one and a half years after the first admission, and at that time she was found to have a very severe organic aciduria while addicted to paraldehyde; the patient has had no aciduria since addiction was cured. Although on no alkali therapy since 1952, there has been only occasional mild depression of serum carbon dioxide level. When tested with 5 day load of ammonium chloride in 1952 following the paraldehyde episode and again in 1956 (as reported on herein) there was still no evidence of osteomalacia or nephrocalcinosis. The patient responded to carbonic anhydrase inhibitor but probably to subnormal extent. She has been reported on in detail previously [20].

CASE II. H. L., a sixty-five year old white housewife, was first seen at Hospital of the University of Pennsylvania in 1952 on the services of Dr. H. Royster and Dr. E. Rose for osteomalacia and multiple fractures. She had recurrent pyelitis for twenty-five years. After onset of pyelitis, weakness, parasthesias and muscle stiffness followed. She had had partial parathyroidectomy ten years before admission; since then she has been crippled with severe pain and weakness in back and legs and has suffered from severe tetany for past year. On admission the patient showed only tenderness over the left thoracic cage and limita-

tion of movement of back and legs. Roentgenograms showed multiple fractures of ribs and spine, generalized osteomalacia, no calcification in kidney, and normal urogram. Serum electrolytes were as follows: carbon dioxide 25.2 mM/L.; chloride 101, sodium 144, and potassium 3.7 mEq./L.; calcium 8.8, phosphorus 1.8, and blood urea nitrogen 12 mg. per cent. Urinalysis showed a specific gravity of 1.003 to 1.010, it was neutral, and 0 to 1 white blood cells.

Six months later the patient was readmitted to the Metabolic Unit for further study. Physical and roentgenographic findings were unchanged. Chemical analyses of serum showed carbon dioxide 20.2 mM/L.; sodium 136, potassium 4.6, and chloride 93 mEq./L.; creatinine 0.7, calcium 8.3, phosphorus 2.1, and blood urea nitrogen 13 mg. per cent. Urinalysis showed white blood cells, positive *Escherichia coli* culture, pH 6.88, HCO_3^- 11 mM/24 hours; phenolsulfonphthalein test was 50 per cent in 25 minutes, 82 per cent in two hours. A five-day ammonium chloride test indicated deficient excretion of titratable acid plus ammonium ion (see text) and an increased excretion of calcium. Acute renal function studies showed $\text{C}_{\text{creatinine}}$ 82, C_{inulin} 91, C_{PAH} 485, C_{PO_4} 23, ml./minute per 1.73 M^2 , TM_{PAH} 89 mg./minute per 1.73 M^2 . Control of the infection of the urinary tract was difficult because of allergic sensitivity to antibiotics. The patient was discharged on vitamin D therapy 2,000 units, dicalcium phosphate, and sodium plus potassium citrate 100 mEq. per day. The subject's course was only moderately satisfactory because of recurrent urinary infection and intermittent dosage of alkali solution. She moved to the West Coast and was last heard of in 1955.

At the time of these admissions the tentative diagnosis was renal tubular acidosis; in retrospect a diagnosis that seems at least as likely is that of resistance to vitamin D complicated by pyelonephritis.

CASE III. A. B., a forty-four year old single white woman, was first admitted in 1953 to the Addenbrooke's Hospital, Cambridge, for study of a generalized flaccid paralysis associated with hypokalemia of two years' duration. Chemical findings in serum were as follows: HCO_3^- 18.7, chloride 116 mEq./L., calcium 9.1, urea 38 mg. per cent. The urine showed a trace of protein, the pH was 7, the specific gravity 1.010 after eighteen hours of fluid deprivation. The clearance of urea was 49 per cent of normal, of endogenous creatinine 53 ml./minute, and phenolsulfonphthalein excretion 50 per cent in two hours. Roentgenographic examination revealed nephrocalcinosis.

Investigations by Fourman and McCance [21] included a three-day ammonium chloride loading test showing deficient excretion of ammonium ion and titratable acid, and a diagnosis of renal tubular acidosis was made. Therapy, however, was rendered difficult because the patient developed tetany when

potassium was administered; the necessary small doses of sodium and potassium citrate barely controlled her acidosis and her subsequent course included progression of nephrocalcinosis with the frequent passing of many stones. In 1957 the patient was readmitted and her acidosis was more completely controlled with sodium and potassium bicarbonate.

CASE IV. M. B., a forty-four year old white woman, was first seen on the service of Dr. R. Mayock in the Hospital of the University of Pennsylvania in 1954, for weakness, polydipsia, polyuria, vomiting and cardiac palpitation. Wasting, tachycardia, heart block, and a diffusely enlarged thyroid were found. Blood chemistry showed the following: serum carbon dioxide 14 mM/L.; sodium 140, chloride 117, and potassium 1.2 mEq./L.; calcium 13.4, phosphorus 3.9, and blood urea nitrogen 29 mg per cent. Urinalysis showed only a trace of albumin and a fixed specific gravity of 1.001 to 1.002. A presumptive diagnosis of hyperthyroidism with secondary hypercalcemia was made and the patient was given methimazole. In March 1955 the patient, clinically improved, was readmitted and a subtotal thyroidectomy was performed. The pertinent blood chemical values were as follows: serum content of carbon dioxide 15 mM/L.; chloride 112, potassium 3.6 mEq./L.; calcium 9.5, phosphorus 2.9, and blood urea nitrogen 15 mg. per cent. A urogram showed bilateral renal calcifications, a finding that had not been present on a similar examination five months previously. Urine concentrated to 1.010 on fluid restriction, urinary pH 7.51, phenolsulfonphthalein was 27 per cent in fifteen minutes and 80 per cent in two hours, and creatinine clearance was 62 ml./minute/ 1.73 M^2 . A diagnosis of renal tubular acidosis was supported by the results of an ammonium chloride loading test and an alkalinizing salt mixture was prescribed.

In 1956 the patient returned because of continued polydipsia and polyuria; alkali therapy had been withheld three weeks. Blood chemical values were essentially as before and an ammonium chloride loading test produced the same results. Alkali therapy was continued. In 1957 the patient again returned with symptoms of hyperthyroidism and was treated with I^{131} . Another ammonium chloride loading test (reported on herein) indicated no change in renal ability to excrete acid. Roentgenograms of the abdomen showed the nephrocalcinosis unchanged. In January 1959 the nephrocalcinosis was again unchanged. The patient was found to have been taking only one-third of the prescribed dose of alkali. This case has been reported previously [22].

CASE V. M. C., a forty-one year old white housewife, was first seen in the Hospital of the University of Pennsylvania in 1956 because of long-standing nephrocalcinosis and nephrolithiasis. At sixteen years of age she first suffered from back pain, chills and fever, and a diagnosis was made of kidney stones. In

1948 a left ureterolithotomy was performed; intravenous pyelography at that time showed no nephrocalcinosis. Until 1953, after the birth of the last of her five children, she had no further symptoms; at this time she again began to pass stones with great frequency. In 1956 a non-toxic adenoma of the thyroid and one normal parathyroid were removed in another hospital. On this admission bilateral nephrocalcinosis was first demonstrated by roentgenograms; a survey of the bones had negative results. Physical examination on admission to the University of Pennsylvania Hospital was essentially within normal limits except for operative scars. Biochemical analyses of blood showed the following: serum content of carbon dioxide 17.8 mM/L.; chloride 113, sodium 141, and potassium 3.6 mEq./L.; calcium 10, phosphorus 2.3, and blood urea nitrogen 16 mg. per cent; alkaline phosphatase 2.4 units. Examination of urine revealed a pH of 6.9, albuminuria 1 plus, 0 to 3 red blood cells, many white blood cells, and a negative culture, phenolsulfonphthalein excretion was 16 per cent in fifteen minutes and 46 per cent in two hours. An ammonium chloride loading test confirmed the diagnosis of renal tubular acidosis. Renal biopsy, performed by Drs. E. A. Hildreth and J. Senior, revealed spotty areas of lymphocytic infiltration, moderate interstitial fibrosis, and a few sclerosed or hyalinized glomeruli; no calcification was seen. Analysis of several renal stones showed that they were composed of calcium carbonate and calcium phosphate. The patient was discharged on a regimen of 50 mEq. of sodium bicarbonate and potassium citrate per day.

During the next six months the patient continued to pass some stones despite an increase in alkali therapy to 130 mEq. cation per day. For a further period of nine months the patient was therefore given sodium phytate, the renal excretion of calcium was decreased but of phosphate increased. By December 1957 the patient's increase in nephrocalcinosis (as shown by roentgenograms) and continued excretion of many stones indicated the undesirability of the phytate therapy; this therapy was stopped and the dose of alkali increased again. In February 1958 two large stones remained impacted in the right ureter and another ureterolithotomy was performed. Following this operation the patient was tested for the renal response to carbonic anhydrase inhibitor and found to respond poorly as compared to normal control subjects; this finding suggested a deficiency of renal carbonic anhydrase [6]. In June 1958, following the increased administration of alkali, the patient's acidosis was controlled and roentgenographic examination suggested that the calcinosis in the right kidney was diminished. In October 1959 the nephrocalcinosis of the right kidney was definitely diminished and the patient was passing very few stones.

Observations on relatives of this patient are reported in the third paper of this series [7].

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The Renal Excretion of Hydrogen Ion in Renal Tubular Acidosis*

II. Quantitative Response to the Carbonic Anhydrase Inhibitor, Acetazolamide

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INHIBITION of the enzyme carbonic anhydrase closely simulates the clinical state of renal tubular acidosis by production of an alkaline urine and a metabolic acidosis. Although this fact has suggested the possibility that deficient activity of carbonic anhydrase is involved in the pathogenesis of this disease [1-3], the evidence for such involvement has been fragmentary and inconclusive. Smith and Schreiner [4] and Gabrielson [5] dismissed the possibility on the basis of finding free hydrochloric acid in the gastric fluid of some of their patients. The enzyme inhibitor, acetazolamide, has been administered to a number of patients with renal tubular acidosis [6-9], including one of our own patients who has already been reported on [7]; in each patient an increase in the rate of excretion of bicarbonate and in urinary pH has been interpreted (correctly) as evidence against the total absence of carbonic anhydrase activity. However, both Reynolds [8] and Frick, Rubini and Meroney [9] recognized that these results were complicated by other factors such as the presence of metabolic acidosis, and considered that carbonic anhydrase activity might well be deficient in renal tubular acidosis.

We believe that the quantitative aspects of the renal response to the administration of acetazolamide have not been examined sufficiently in these patients. For such an examination we have adopted the test used by Kaye [6], namely the change in excretion rate of bicarbonate and of hydrogen ion during the second and third hours

after the administration of a single dose of acetazolamide, and have corrected the results for body size to a standard surface area. Four of our patients with renal tubular acidosis have been compared, while on alkali therapy, with a group of normal subjects either on normal diets or receiving sodium bicarbonate or ammonium chloride, and with a group of patients with generalized renal diseases such as chronic glomerulonephritis and nephrosclerosis. In both the patients with renal tubular acidosis and the patients with generalized renal disease, the administration of acetazolamide produced a smaller increase in excretion of bicarbonate than in the normal non-acidotic subjects. But analysis of changes in bicarbonate excretion and bicarbonate reabsorption relative to bicarbonate concentration in serum and filtered load indicates that this use of the enzyme inhibitor has not demonstrated conclusively diminished enzyme activity in these patients with either type of renal disease.

MATERIALS AND METHODS

The response (acute) to the administration of acetazolamide was measured in ten normal adult men on normal diets, in three when loaded with bicarbonate, and in two when loaded with ammonium chloride; it was also measured in eight patients with renal disease. Four of these patients had generalized renal disease of the type that progresses to contracted kidneys (chronic glomerulonephritis, chronic pyelonephritis, nephrosclerosis); however, metabolic acidosis had not as yet developed. Short case histories of

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TABLE I
RENAL RESPONSE TO THE ADMINISTRATION OF A STANDARD SINGLE DOSE OF ACETAZOLAMIDE
IN NORMAL SUBJECTS

Subject*	Acetaz- olamide (mg.)	Urine					Serum Bicarbon- ate (mEq. per L.)	Creati- nine Clearance (ml. per min.)	Bicarbon- ate Filtered (μEq. per min.)	Bicarbon- ate Reabsorbed (mEq. per L. filtrate)	Change in		
		pH	Bicarbon- ate (μEq. per min.)	Titrate- ble Acidity (μEq. per min.)	NH ₄ ⁺ (μEq. per min.)	H ⁺ (μEq. per min.)					Bicarbon- ate Reabsorbed (mEq. per L. filtrate)	Bicarbon- ate Excreted (μEq. per min.)	H ⁺ Excreted (μEq. per min.)
G. W. 1.98	0 655	6.93 7.85	23 404	16 0	15 6	8 -375	(28.4)	124 113	3510 2945	...	-6.2	+381	-390
L. I. 1.84	0 648	6.32 7.70	16 274	11 0	39 7	34 -267	(25.3)	128 113	3225 2610	...	-4.7	+258	-301
R. E. ₁ 1.89	0 686	6.95 7.50	36 241	6 0	15 4	-15 -237	(25.0)	109 92	2715 2100	...	-4.7	+205	-222
J. M. 1.90	0 682	6.15 7.63	4 290	8 0	30 5	34 -285	(25.0)	131 113	3265 2575	...	-5.0	+286	-319
E. H. ₁ 1.93	0 672	7.18 7.62	95 363	2 0	13 9	-80 -354	27.8 26.8	126 104	3488 2785	27.1 23.2	-3.9	+268	-274
L. R. 1.85	0 688	7.60 7.66	77 378	0 0	21 5	-56 -373	26.4 24.3	111 101	2930 2455	25.7 20.5	-5.2	+301	-317
W. R. 2.16	0 651	6.12 7.99	22 230	8 0	22 3	8 -227	27.4 21.6	118 118	3230 2550	27.2 19.7	-7.5	+208	-235
H. S. ₁ 1.83	0 650	6.29 7.89	9 386	10 0	36 4	37 -382	28.4 25.2	114 95	3236 2395	28.3 21.2	-7.1	+377	-419
H. S. ₂ 1.83	0 650	7.04 8.00	35 583	3 0	23 5	9 -578	26.2 23.2	107 92	2803 2118	25.9 16.7	-9.2	+548	-569
W. J. ₁ 1.92	0 675	6.30 7.69	18 349	12 0	22 4	16 -345	26.3 25.6	94 89	2475 2280	26.2 21.7	-4.5	+331	-361
W. J. ₂ 1.92	0 675	7.65 7.81	110 414	0 0	6 4	-104 -410	28.4 26.9	101 89	2870 2395	27.3 22.4	-4.9	+304	-306
C. B. ₁ 1.98	0 709	6.00 7.69	4 256	17 0	23 4	36 -252	26.8 25.7	90 80	2410 2060	26.7 22.5	-4.2	+252	-288
C. B. ₂ 1.98	0 709	7.49 7.93	145 399	0 0	7 4	-138 -395	27.1 25.7	102 86	2825 2206	26.3 21.1	-5.2	+254	-357
mean:											-5.6	+306	-328

NOTE: All data are corrected to a standard surface area of 1.73 M²; the values in parentheses are assumed from prior determinations; for each subject the data as presented are the averages for two periods (one-hour each) before the administration of acetazolamide and for the second and third hour after the drug.

* Data under subjects initials indicate surface area in M².

these patients are appended at the end of this paper. The other four patients with "non-contracted" kidneys were diagnosed clinically as having renal tubular acidosis (RTA). Three of these patients with RTA (M. C., M. B. and A. B.) exhibited the classic form of the disease, namely, metabolic acidosis without azotemia, with relatively alkaline urines, and with associated nephrocalcinosis; the other patient with RTA (A. T.) was able to produce a more acid urine but failed to excrete a normal total amount of hydrogen ion associated with a low excretion rate of phosphate. These four patients with RTA constituted the main portion of the group tested for their response to the administration of ammonium chloride as reported

in the preceding paper [10], and their case histories are summarized there.

The test was conducted as follows. On a liberal intake of fluid to ensure a diuresis, a timed urine collection was made during each of five consecutive hours. Two of the patients with RTA were catheterized and their bladders were washed; the normal subjects and other patients emptied their own bladders in the upright position. At the end of the second hour a single dose of acetazolamide was administered, 10 mg./kg. of body weight, a dose which ranged between 446 and 810 mg./1.73 M² of surface area. With the exception of one normal subject (E. H.) and one patient (A. T.) the drug was given orally; in the subjects

TABLE II
RENAL RESPONSE TO THE ADMINISTRATION OF A STANDARD SINGLE DOSE OF ACETAZOLAMIDE
IN PATIENTS WITH RENAL TUBULAR ACIDOSIS AND WITH GENERALIZED RENAL DISEASE

Subject*	Acetaz- solamide (mg.)	Urine					Serum Bicarbon- ate (mEq. per L.)	Creati- nine Clearance (ml. per min.)	Bicarbon- ate Filtered (μEq. per min.)	Bicarbon- ate Reabsorbed (mEq. per L. filtrate)	Change in		
		pH	Bicarbon- ate (μEq. per min.)	Titrateable Acidity (μEq. per min.)	NH ₄ ⁺ (μEq. per min.)	H ⁺ (μEq. per min.)					Bicarbon- ate Reabsorbed (mEq. per L. filtrate)	Bicarbon- ate Excreted (μEq. per min.)	H ⁺ Excreted (μEq. per min.)
Patients with Renal Tubular Acidosis													
A. T. 1.51, 54.9	0 573	6.00 7.48	28 167	18 0	33 7	23 -160	24.2 (23.6)	102 101	2470 2370	24.0 22.0	-2.0	+139	-183
M. C. ₁ 1.48, 56.3	0 609	6.83 7.40	21 57	10 5	19 10	8 -42	24.0 24.0	68 56	1632 1343	23.8 22.9	-0.9	+36	-50
M. C. ₂	0 609	7.07 7.31	29 84	4 2	6 5	-19 -77	21.2 20.1	57 50	1198 995	20.6 18.5	-2.1	+51	-57
M. C. ₃	0 609	7.68 7.65	71 210	0 0	2 2	-69 -208	22.0 (21.4)	75 65	1639 1430	21.1 18.2	-2.9	+139	-139
M. B. 160, 60.0	0 703	6.79 7.55	13 150	8 0	14 7	9 -143	18.0 17.2	82 78	1476 1341	17.8 15.3	-2.5	+137	-152
A. B. 160, 60	0 810	8.15 8.20	69 277	0 0	...	(69) (277)	28.5 27.5	42 42	1197 1160	26.8 21.0	-5.8	+208	-208
mean:											-2.7	+118	-132
Patients with Generalized Renal Disease													
J. G. 1.60, 56.4	0 ...	6.20 7.25	1 35	10 2	3 3	12 -30	21.5 23.7	20 24	430 557	21.4 21.7	+0.3	+32	-42
J. D. 194, 71.0	0 ...	6.70 7.65	6 106	6 0	10 1	10 -107	24.1 23.8	65 47	1566 1168	24.0 22.4	-1.4	+100	-117
H. S. 194, 79.1	0 446	5.75 7.47	3 101	21.4 20.3	85 76	1820 1544	21.4 19.0	-2.4	+98	...
D. B. 184, 68.4	...	7.18 7.52	24 150	1 0	7 6	-16 -144	26.0 24.2	69 60	1794 1439	25.7 21.7	-4.0	+126	-128
mean:											-1.9	+89	-96

* Data under each subjects initials indicate surface area in M² and weight in kilograms, respectively.

TABLE III
RENAL RESPONSE TO THE ADMINISTRATION OF A STANDARD SINGLE DOSE OF ACETAZOLAMIDE
IN NORMAL SUBJECTS LOADED WITH NH₄CL

Subject	Acetaz- olamide (mg.)	Urine					Serum Bicarbon- ate (mEq. per L.)	Creati- nine Clearance (ml. per min.)	Bicarbon- ate Filtered (μ Eq. per min.)	Bicarbon- ate Reabsorbed (mEq. per L. filtrate)	Change in		
		pH	Bicarbon- ate (μ Eq. per min.)	Titrateable Acidity (μ Eq. per min.)	NH ₄ ⁺ (μ Eq. per min.)	H ⁺ (μ Eq. per min.)					Bicarbon- ate Reabsorbed (mEq. per L. filtrate)	Bicarbon- ate Excreted (μ Eq. per min.)	H ⁺ Excreted (μ Eq. per min.)
R. E. ₂ 1.89	0 686	4.72 6.95	0 57	26 14	47 11	73 -32	20.3 20.5	91 77	1847 1579	20.3 19.8	-0.5	+57	-105
E. H. ₂ 1.92	0 700	5.13 7.50	0 128	29 0	89 40	106 -88	21.9 20.0	123 88	2683 1760	21.9 18.6	-3.3	+128	-102

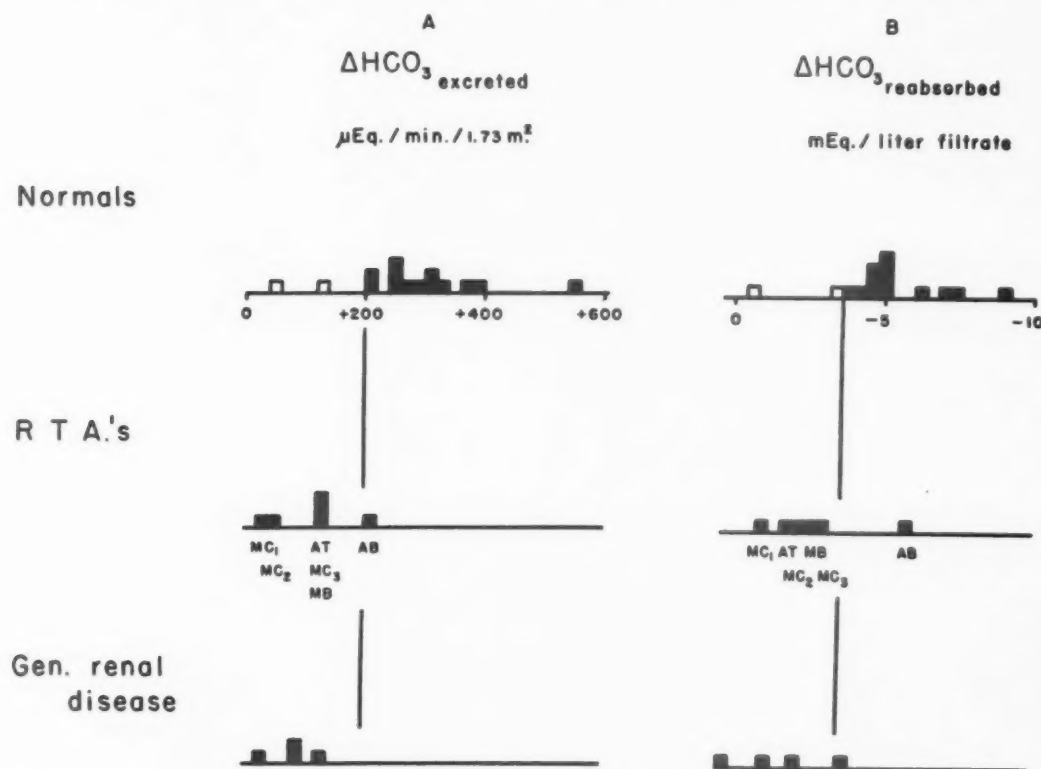


FIG. 1. Response to the administration of a single standard dose of acetazolamide in normal subjects, in patients with RTA, and in patients with generalized renal disease. Open squares are normal subjects loaded with ammonium chloride for three days. Initials identify the patients with RTA. Patients with both kinds of renal disease show a lesser response to the enzyme inhibitor than do the non-acidotic normal subjects.

in whom the drug (in 5 per cent glucose solution) was administered intravenously, the rate of response did not appear to differ significantly from that in the other subjects and patients. Blood for analysis was drawn at the end of the control period and at the third hour after the administration of acetazolamide.

Each urine specimen was collected under mineral oil and toluene, and was immediately analyzed, using anaerobic techniques, for total carbon dioxide, pH, titratable acidity, ammonium ion, as well as for chloride, sodium, potassium, magnesium, calcium, phosphate and creatinine. Serum was analyzed for carbon dioxide and creatinine. The chemical methods used are described in the preceding paper [10]. The bicarbonate concentration in serum was calculated in milliequivalents per liter from the total carbon dioxide content in mM per liter by subtracting the value 1.3, the assumed concentration of carbonic acid.

The rate of excretion of hydrogen ion was calculated from the excretion rates of titratable acid, ammonium ion, and bicarbonate (as shown in Equation 1 of the first paper of this series). The average rates of excretion of hydrogen ion and bicarbonate during the second and third hour after the administration of acetazolamide were then compared with the average rates from the two control periods; and the difference

expressed in microequivalents per minute per 1.73 M^2 . Using the value for the endogenous creatinine clearance as equivalent to the rate of glomerular filtration, the amount of bicarbonate filtered per unit time and hence the rate of reabsorption of bicarbonate were calculated for the periods before and after the administration of acetazolamide. The rates were likewise given in units of microequivalents per minute per 1.73 M^2 ; in addition, the reabsorption of bicarbonate was also expressed in terms of milliequivalents per liter of glomerular filtrate.

At the time of testing with the administration of acetazolamide, one patient with RTA (A. T.) was maintaining an essentially normal serum level of bicarbonate without alkali therapy [7]. A second patient (M. C.) at the time of the first test was on an uncertain daily dose of sodium and potassium citrate but had a normal serum concentration of bicarbonate; at the times of the second and third tests she was receiving 66 and 164 mEq. daily, respectively, of these salts and her concomitant serum contents of total carbon dioxide were just within the lower 2 minus standard deviation range of our normal subjects (see Table II, [10]). A third patient (M. B.) was on inadequate alkali dosage and had a somewhat lowered serum bicarbonate concentration; the fourth

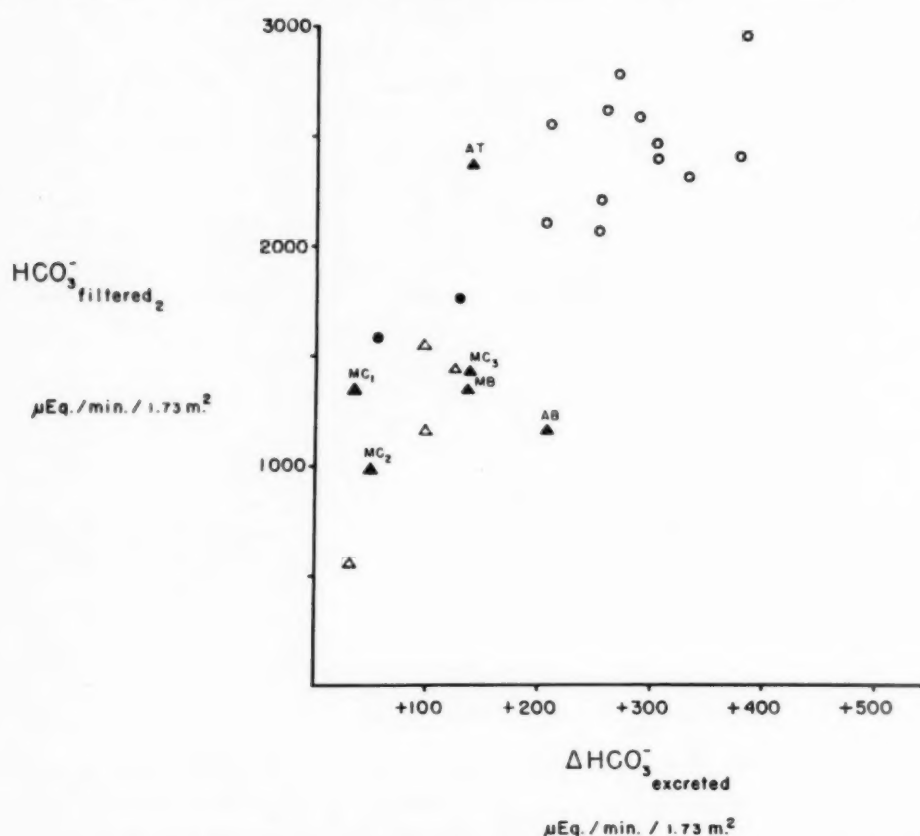


FIG. 2. Relation of change in the absolute rate of bicarbonate excretion, following the administration of acetazolamide, to the concurrent rate of glomerular filtration of bicarbonate. Open circles represent normal non-acidotic subjects, solid circles normal subjects made acidotic with ammonium chloride; open triangles indicate patients with generalized renal disease and solid triangles patients with renal tubular acidosis. Change in bicarbonate excretion varies with the amount of bicarbonate filtered, and in this respect there is no clear differentiation between the normal subjects and the patients with either type of renal disease.

patient (A. B.) on alkali therapy exhibited a high normal serum level of bicarbonate. As a control for alkali therapy three of our normal subjects (H. S., W. J. and C. B.) were retested after the ingestion of supplementary amounts of sodium bicarbonate for two days prior to the second test. For comparison with the patients with slightly depressed serum bicarbonate levels two of the normal subjects (E. H. and R. E.) were tested again on the third day of ingesting a daily dose of 6 gm. of ammonium chloride.

RESULTS

The results are presented in Tables I through III and in Figures 1 through 3.

During the second and third hour after the administration of a single dose of acetazolamide all the normal subjects and patients, with and without RTA, excreted a urine which was less acid; the excretion rates of titratable acid and of ammonium ion fell and that of bicarbonate rose,

as did the urinary pH (Tables I and II). Quantitatively, the greatest change was in the excretion rate of bicarbonate and this was reflected in the fall in the calculated excretion rate of total hydrogen ion. However, these changes were less in the patients with RTA than in the non-acidotic normal subjects. In the latter the mean changes in excretion rate of bicarbonate and of hydrogen ion, respectively, were plus 306 and minus 328 $\mu\text{Eq.}/\text{minute}/1.73 \text{ M}^2$ and the corresponding minimum values were plus 205 and minus 222. In the patients with RTA the change in bicarbonate excretion ranged between plus 36 and plus 208, and in hydrogen ion excretion between minus 50 and minus 208, $\mu\text{Eq.}/\text{minute}/1.73 \text{ M}^2$. Thus, there was a great difference in distribution of the response of these excretory rates to the enzyme inhibitor between the non-acidotic normal subjects and the patients with

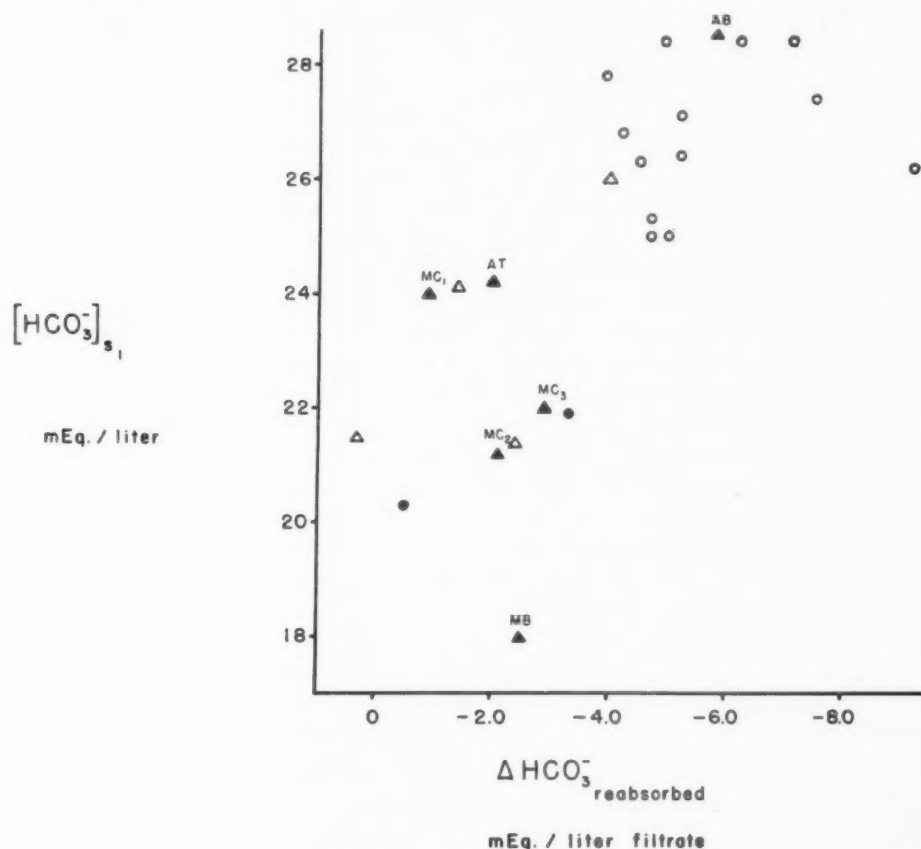


FIG. 3. Relation of change in the tubular reabsorption of bicarbonate per unit of filtrate, following the administration of acetazolamide, to the initial concentration of bicarbonate in serum. Symbols are as in Figure 2. A positive correlation obtains in all three groups of subjects and patients.

RTA. (Fig. 1A.) The changes in these excretory rates in the acid-loaded normal subjects, however, were lower and within the range of the patients with RTA. In the four patients with generalized renal disease the changes in rate of excretion of bicarbonate and of hydrogen ion ranged between plus 32 and plus 126 and minus 43 and minus 128 $\mu\text{Eq.}/\text{minute}/1.73 \text{ M}^2$, respectively, and thus were not greatly different from the patients with RTA.

The serum bicarbonate concentration, when measured after the administration of the drug fell in all the non-acidotic normal subjects and in most of the patients. (Tables I and II.) One patient (M. B.) had the lowest serum bicarbonate level at the end of any test (17.2 mEq./L.). The clearance of endogenous creatinine fell uniformly after the administration of acetazolamide in most of the subjects and patients. In the normal subjects the control values for creatinine clearance ranged between 90 and 131 ml./minute/1.73 M^2 . In one patient (A. T.)

clearance fell within this range (102); a patient with RTA (M. C.) exhibited lower clearances (68, 57 and 75) as did other patients with RTA (M. B. and A. B.) whose clearances were, respectively, 82 and 42 ml. per minute/1.73 M^2 . In the four patients with generalized renal disease creatinine clearances ranged from 20 to 85 ml./minute/1.73 M^2 .

The change in rate of tubular reabsorption of bicarbonate after the administration of acetazolamide was less in three of the four patients with RTA than in the non-acidotic normal subjects whether expressed in relative units of milliequivalents per liter of glomerular filtrate (Fig. 1B) or in absolute units of microequivalents per minute per 1.73 M^2 . In relative units the change in bicarbonate reabsorption in the non-acidotic normal subjects was minus 3.9 to minus 9.2, in the patients with RTA minus 0.9 to minus 5.8 mEq./L. of glomerular filtrate. In both the acid-loaded normal subjects and three of the four patients with generalized disease the

change in bicarbonate reabsorption relative to glomerular filtrate was below the range of the non-acidotic normal subjects and similar to that of the patients with renal tubular acidosis.

COMMENTS

Interpretation of the Results. The response of these patients with renal tubular acidosis to the administration of acetazolamide must be interpreted with caution. Observation of a lessened response to inhibition of an enzyme is not necessarily evidence that the activity of that enzyme is deficient. Furthermore, factors other than enzyme activity are involved in this particular physiological response. Hence such an interpretation requires some consideration of what is known about carbonic anhydrase and exchanges of hydrogen ion in the renal tubule.

Data relating to the presence of carbonic anhydrase in the renal tubule and its role in facilitating hydrogen ion exchange have been reviewed extensively [2,11,12]. Whether this facilitation is accomplished by hydration of carbon dioxide to carbonic acid or by its hydroxylation to bicarbonate, the net result is the same, namely to make protons available for exchange. The demonstrations by Berliner, Kennedy and Orloff [13] and Schwartz and Relman [14] that massive doses of the enzyme inhibitor, acetazolamide, lead to excretion of 33 to 80 per cent of filtered bicarbonate indicates that carbonic anhydrase is active in the proximal as well as in the distal tubule. The view that all bicarbonate reabsorption takes place by a process of ion exchange requiring carbonic anhydrase activity has been challenged by Hanley and co-workers [15]; these workers found the reabsorption of only 21 to 29 per cent of filtered bicarbonate to be inhibited by acetazolamide in man. Nevertheless ion exchange must be involved in at least part if not all of the proximal tubular reabsorption of bicarbonate. According to Pitts [16], the hydrogen ions thus made available in the proximal tubule diffuse outward passively secondary to the active inward transport of sodium; in the distal tubule hydrogen and potassium compete in a coupled pump which also is moving sodium actively inward. Hence inhibition of carbonic anhydrase activity blocks the reabsorption of bicarbonate in both segments of the nephron; in the distal tubule it inhibits the acidification of phosphate buffers and enhances potassium excretion as well.

Factors other than the activity of carbonic

anhydrase also determine the extent of hydrogen ion exchange and the reabsorption of bicarbonate. Changes in PCO_2 have been shown to operate [17-19] and indeed a rise in PCO_2 will override the inhibition of carbonic anhydrase, as Brazeau and Gilman have shown experimentally [12,17]. In metabolic acid-base disturbances which are acute the excretion rates of hydrogen ion and of bicarbonate vary inversely and directly, respectively, with extracellular fluid pH [20]. The reabsorption of bicarbonate varies with the PCO_2 but, because of the very large changes in the filtered load, not with the excretion of bicarbonate. Thus we have the paradoxical situation that in severe metabolic acidosis, when extracellular pH is low, tubular secretion or transport of hydrogen ion is diminished, i.e., less bicarbonate is filtered and less hydrogen ion is exchanged for its reabsorption.

Metabolic acidosis is well known to override the action of acetazolamide and to prevent the excretion of bicarbonate [6,17]. However, in a critical series of experiments, Schwartz, Falbriard and Relman [27] have demonstrated that the administration of larger doses of acetazolamide (5 to 20 mg./kg.) do have an effect in acidotic dogs even in the most severe degrees of metabolic acidosis. The data in their experiments were analyzed in terms of Michaelis-Menten enzyme kinetics. The conclusion was reached that when the serum bicarbonate level is about 25 mEq./L. or lower, substrate presentation (bicarbonate filtered) and/or other factors such as PCO_2 limit the total reabsorption of bicarbonate in the absence of inhibition of carbonic anhydrase; but in the presence of carbonic anhydrase inhibition the enzyme is the rate limiting factor.

These experimental findings would lend support to an interpretation of our own observations of our patients with renal tubular acidosis, namely, that deficient renal carbonic anhydrase activity is rate limiting and is responsible for the quantitatively smaller response to the inhibition of acetazolamide. But the responses in our patients with both types of renal disease were conditioned by variation both in filtered load and in serum concentration of bicarbonate. In Figure 2 it is shown that the change in the absolute rate of excretion of bicarbonate, following enzyme inhibition, varies with the rate of filtration of bicarbonate and that this relationship is not different between the normal subjects (non-acidotic and acidotic) and either

group of patients. A large part of the decrease in filtration of bicarbonate was due to lowering of the glomerular filtration rate rather than to lowering of the serum level of the ion. However, as shown in Figure 3, when on enzyme inhibition the serum concentration of bicarbonate is related to the change in bicarbonate reabsorbed per unit of glomerular filtrate, it is apparent that as the bicarbonate level falls the effect of acetazolamide is diminished to the same extent in all groups. We can only conclude that carbonic anhydrase inhibition, at least at this dose level, does not demonstrate definitively the presence or absence of deficient activity of the enzyme in either group of renal patients. The pathogenesis of renal tubular acidosis has not yet been shown to involve a specific enzymatic defect.

Proton Donation in Renal Tubular Acidosis. Factors in the pathogenesis of renal tubular acidosis already have been considered in the first paper of this series [10] where it is pointed out that in at least the classic type, in which systemic acidosis is associated with a relatively alkaline urine, mechanisms of tubular proton donation appear to be principally at fault. Hence we attempted to examine one factor in tubular proton donation, namely, the activity of carbonic anhydrase. These studies supplement other physiological maneuvers that have been made in an effort to clarify the pathogenesis of this disease. Latner and Burnard [22], and subsequently a series of other investigators [4,8,9,23,24] administered phosphate to patients with RTA and found that, although the change in urinary pH was slight and variable, the excretion rate of titratable acidity always increased. Thus more hydrogen ions can be transferred when more proton acceptors, as phosphate buffer, are supplied; Pitts and co-workers [25] had shown this to be true in normal subjects. The administration of bicarbonate loads to patients with RTA has also been found to increase the tubular reabsorption of bicarbonate and hence the tubular exchange of hydrogen ion [4,8,9]. Both experiments might be interpreted to indicate that there is a deficit of proton acceptors in the tubular urine in these patients. But, as Mudge has pointed out [3], supplying such acceptors still does not enable the normal transfer of hydrogen ions against a concentration gradient in patients with RTA.

As indicated previously [10,26], not all patients with acidosis due to disease of a non-contracted kidney necessarily have a defect in tubular

proton donation; in some such patients factors of proton acceptor deficiency (phosphate or ammonia) appear to be primary. But, as already stated, in the conventional type of renal tubular acidosis the primary defect apparently does lie in the process or processes of proton donation, i.e., the production of hydrogen ion in and/or the transfer of hydrogen ion from the tubular cells. Presumably proton donation is defective in proximal as well as in distal segments of the tubule. While it is recognized that adrenocortical steroids condition the active reabsorption of sodium in the proximal tubule and may therefore, increase the outward exchange of hydrogen ion [27], there is no evidence that patients with renal tubular acidosis have a defective response to salt-retaining steroids which might result in a diminished exchange and excretion of hydrogen ion. Hydrogen ion transport against a gradient or hydrogen ion production appears to be at fault, and the latter is closely conditioned by the enzyme carbonic anhydrase. The evidence presented in this paper does not rule in deficient activity of carbonic anhydrase as a factor in the pathogenesis of renal tubular acidosis, nor does it rule it out. Perhaps another investigative approach can be designed to elucidate the role of this enzyme in these patients. It is possible that other disturbances are involved in the metabolic processes that supply the energy for the active tubular transport of hydrogen. The problem warrants further study.

SUMMARY

A single test dose of the carbonic anhydrase inhibitor, acetazolamide, was given to ten normal non-acidotic subjects, two normal subjects made acidotic with ammonium chloride, four patients with renal tubular acidosis, and four patients with generalized renal disease. Changes relative to the control level were measured in the renal excretion of bicarbonate and of total hydrogen ion during the second and third hour after the administration of the drug, and the changes in the tubular reabsorption of bicarbonate were calculated.

Changes in the rate of excretion of bicarbonate and in the tubular reabsorption of bicarbonate per unit of glomerular filtrate were diminished relative to the non-acidotic normal subjects in most of the patients with both types of renal disease; there was no difference relative to the normal subjects made acidotic with ammonium chloride.

The change in rate of excretion of bicarbonate following enzyme inhibition varied with the filtered load of bicarbonate, and to the same extent in all groups; the same was true with respect to the relation of the serum bicarbonate concentration to the amount of bicarbonate reabsorbed per unit of glomerular filtrate.

It is concluded that these observations are consistent with, but neither rule in nor rule out, deficient activity of carbonic anhydrase as one factor in the tubular impairment of proton donation in renal tubular acidosis.

Acknowledgment. The authors are grateful to the following colleagues who joined us in serving as experimental subjects: Drs. C. Brooks, L. Isaacson, W. Jones, W. Rambo, L. Rubin, H. Shute and Mr. J. Mitchell. We are indebted also to the members of the laboratory staffs of the Chemical Section of the Department of Medicine, University of Pennsylvania, and the Department of Experimental Medicine, University of Cambridge.

APPENDIX

The following brief summaries of patients with generalized renal disease are presented:

CASE I. J. G., a fifty-seven year old Negro man, was admitted twice to the Hospital of the University of Pennsylvania. On the first admission in 1950, at forty-eight years of age, for hyperthyroidism and subtotal thyroidectomy, a diagnosis of subacute glomerulonephritis was made on the basis of elevated sedimentation rate, albuminuria, and red cells and granular casts in the urinary sediment. At that time phenolsulfonphthalein excretion was 60 per cent in thirty minutes and 80 per cent in two hours; blood urea nitrogen serum creatinine and blood pressure (130/70 mm. Hg) were normal. The second admission to the Hospital of the University of Pennsylvania in 1958 was for exertional dyspnea, palpitation, edema of the ankles, nocturia and polyuria. The blood pressure was 190/80 mm. Hg, grade 2 sclerotic changes in the fundi, pulmonary basilar rales, cardiac enlargement and edema below the tibia were found. Laboratory studies revealed the following: hemoglobin 7.5 gm. per cent; blood urea nitrogen 32, creatinine 3.8, calcium 7.7, PO_4 5.8 mg. per cent; carbon dioxide 22.5 mM/L.; sodium 141, potassium 3.7, chloride 114 mEq./L. Urinary sediment showed albumin, red cells and granular casts. Phenolsulfonphthalein excretion was 4 per cent in fifteen minutes, 25 per cent in two hours. Intravenous urogram showed no excretion of dye until three hours after injection, but kidney shadows were normal in size. Diagnosis, despite the hyperchloremia and mild azotemia, was chronic glomerulonephritis.

CASE II. J. D., a forty-four year old Negro man, was admitted to the Hospital of the University of Pennsylvania in 1959 for a left inguinal herniorrhaphy. He was found to have hypertension (190/130 mm. Hg), grade 2 arteriosclerotic and hypertensive changes in the fundi, and cardiac enlargement. Laboratory studies showed the following: hemoglobin 15.1 gm. per cent; blood urea nitrogen 24, serum creatinine 2.1 mg. per cent; carbon dioxide 25.4 mM/L.; sodium 140; potassium 4.8; chloride 103 mEq./L. Urinalysis showed albumin, a specific gravity of 1.021, and hyaline casts. Phenolsulfonphthalein excretion was 5 per cent in fifteen minutes and 45 per cent in two hours. Intravenous urogram showed blunting of the calyces bilaterally but normal excretion of dye. Urine culture was positive for alpha streptococcus and hemolytic *Staphylococcus albus*. Diagnosis was essential hypertension with nephrosclerosis and chronic pyelonephritis.

CASE III. H. S., a thirty-two year old Negro man, was admitted in 1955 to the Hospital of the University of Pennsylvania for headache, dyspnea, and edema of face and feet of five days' duration. There was a history of chronic otitis media and intermittent pain in the left flank for several years. The blood pressure was 140/90 mm. Hg. There was periorbital and sacral edema. Laboratory studies showed the following: hemoglobin 13.1 gm. per cent; corrected sedimentation rate 39 mm. per hour; blood urea nitrogen 39, creatinine 2, calcium 8.4, PO_4 4.4 mg. per cent; sodium 140, chloride 108, potassium 5.4 mEq./L.; carbon dioxide 24.5 mM/L.; albumin 1.1, globulin 3.1 gm. per cent. Urinalysis showed 4 plus albuminuria, red cells, many fine and cellular granular casts. Intravenous urogram revealed no abnormalities. The diagnosis was acute exacerbation of chronic glomerulonephritis.

CASE IV. D. B., a fifty-four year old Negro man, was admitted to the Hospital of the University of Pennsylvania in 1959 with acute symptoms of myocardial infarction. Pertinent findings relative to the kidney were a history of nocturia for many years and occasional bilateral pain in the flank for three months' duration, a markedly enlarged heart, hypertension (144/105 mm. Hg), albuminuria (4 plus and occasional granular casts), and the following laboratory findings: blood urea nitrogen 28, creatinine 1.9, calcium 9.5, PO_4 3.2 mg. per cent; hemoglobin 11.6 gm. per cent, carbon dioxide 27.4 mM/L., sodium 130, chloride 101, potassium 5.9 mEq./L. Phenolsulfonphthalein excretion 10 per cent in one hour and 25 per cent in two hours. Renal diagnosis was nephrosclerosis.

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The Renal Excretion of Hydrogen Ion in Renal Tubular Acidosis*

III. An Attempt to Detect Latent Cases in a Family; Comments on Nosology, Genetics and Etiology of the Primary Disease

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IN the preceding papers [1-3] evidence has been presented that more than one physiological mechanism may be involved in the pathogenesis of renal acidosis without progressive and destructive renal disease. Consideration of the etiology of these disturbances has posed the problem of whether or not we are dealing with one or more than one homogeneous disease state, i.e., the nosology of this type of renal acidosis which has been reported in such a wide variety of clinical circumstances.

These clinical circumstances may be briefly recapitulated. In 1936 Butler, Wilson and Farber [4] first described an acidosis occurring in children with diffuse nephrocalcinosis. In 1945 Baines, Barclay and Cooke [5] reported on an adult patient with this syndrome. In 1946 Albright et al. [6] published their monograph on osteomalacia and late rickets; in this study a group of their patients with osteomalacia also had nephrocalcinosis and metabolic acidosis. Their diagnostic label for this group was *tubular insufficiency without glomerular insufficiency*. This rather cumbersome term has been replaced by the generally accepted one of *renal tubular acidosis*, as suggested by Pines and Mudge in 1951 [7]. If one accepts the all-inclusive definition of renal tubular acidosis as an impairment of the ability of the kidney to excrete acid out of proportion to the impairment of glomerular filtration, this particular renal dysfunction has since been found in various age groups and often

in association with other specific abnormalities of renal tubular transport. The clinical occurrences of renal tubular acidosis may be grouped as follows: (1) in infantile hyperchloremic acidosis in which, if therapy is adequate, recovery usually occurs by the age of twenty-four months; (2) in older children and adults, usually with nephrocalcinosis and nephrolithiasis and with or without osteomalacia or rickets; (3) in children and adults with associated glycosuria and aminoaciduria (the de Toni-Fanconi syndrome); (4) in infants and young children with concomitant cataracts and mental retardation (Lowe's syndrome); (5) in a group of miscellaneous inborn errors of metabolism such as galactosemia, nephrogenic diabetes insipidus and Wilson's disease; and (6) in a certain number of patients with pyelonephritis. Considering the multiplicity of clinical settings or syndromes in which this type of renal acidosis is found, it is not surprising that there is some question as to the identity of the defect as a disease process, let alone its etiology.

Our approach to this problem, in the study of our patients and in an analysis of the cases reported in the literature, has been to exclude those cases with the multiple defects in tubular reabsorption of glucose and aminoacids (de Toni-Fanconi), those with mental retardation (Lowe), those with other primary inborn metabolic defects, and those with generalized renal damage due to chronic pyelonephritis. But even after the

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exclusion of these four groups of patients, the homogeneity of the first two groups of infant and adult renal tubular acidosis is not clear. Hereinafter, the disease in these two groups will be referred to as *primary renal tubular acidosis*.

The reported occurrence in twelve families of overt primary renal tubular acidosis in more than one sibling, or of nephrocalcinosis, nephrolithiasis or osteomalacia in one or more relatives, clearly suggests that a genetic factor is involved in the cause of this syndrome. If so, some relatives may harbor a latent or subclinical defect in renal acid excretion. As in certain other genetic metabolic diseases, such as phenylketonuria and galactosemia, detection of such a latent impairment by a provocative test or physiological challenge would be necessary for adequate study of the genetics, and of the nosology, of the syndrome.

In this paper we present a report of an attempt to detect subclinical impairment of renal acid excretion in relatives of a typical patient with adult primary renal tubular acidosis. From the data of this family and from a survey of the clinical patterns in previously reported cases we conclude that the syndrome consists of two separate disease entities, as presented in the first two groups, and that genetic factors are of prime importance in the etiology of at least one of these entities.

RESULTS OF A FAMILY STUDY

Experimental Material. Ten close relatives of our patient (M. C.), a woman with renal tubular acidosis, were studied. The detailed case history of M. C. and the studies which supported the diagnosis of renal tubular acidosis in this patient appear in the first paper of our series [2]. The main clinical features of the case may be recapitulated. M. C., a forty-one year old white housewife, had a twenty-five year history of nephrolithiasis, roentgenographic evidence of extensive bilateral nephrocalcinosis in kidneys of normal size (Fig. 1), and the chemical findings of metabolic acidosis without azotemia in the presence of a relatively alkaline urine. In addition the patient showed an abnormally low hydrogen ion "clearance" index on a test load of ammonium chloride [2] and a quantitatively low response to the administration of carbonic anhydrase inhibitor, acetazolamide, while on adequate alkali therapy [3].

A genetic factor in the etiology of renal tubular acidosis in this patient is suspected on the following grounds. The patient's father (J. T.) was found to have a large staghorn calculus, parenchymal calcification and hydronephrosis in one kidney. One of the

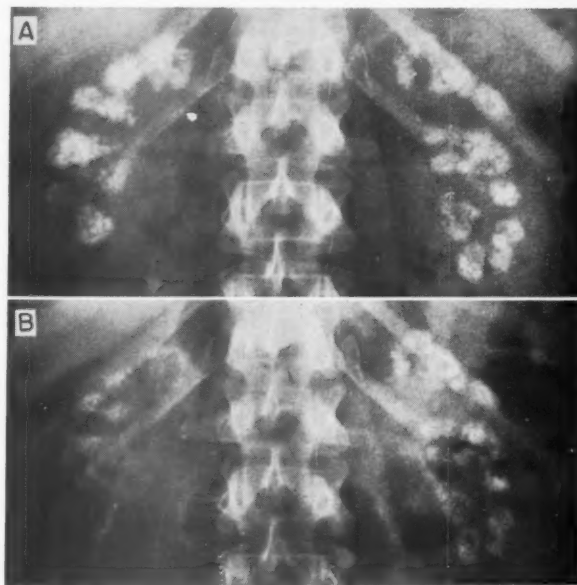


FIG. 1. Nephrocalcinosis in patient (M. C.) with renal tubular acidosis. Roentgenograms taken two and a half years apart (A, March 1957, B, October 1959) show diminution in calcification after intensive alkali therapy.

patient's three brothers and three of her five children showed serum levels of carbon dioxide below the normal range on one or more occasions, although none of the children, and neither of the two brothers with normal carbon dioxide levels, had clinical symptoms or roentgenographic evidence of nephrolithiasis or nephrocalcinosis. The brother with the low serum carbon dioxide (W. T.) has not admitted to symptoms and has refused to permit roentgenographic examination of his abdomen and kidneys or any further physiological studies.

To test the two brothers (who cooperated in this study) and the three mildly acidotic children for subclinical impairment of renal ability to excrete acid, ammonium chloride was given for three days, and the renal response assessed by calculation of the hydrogen ion "clearance" index as described in a preceding paper [2]. Some of these relatives also were tested for their quantitative response to the administration of acetazolamide [3]. The family relationships are shown in Figure 2. There is no family history of consanguinity.

Blood Studies. The blood data are presented in Table 1. Venous serum carbon dioxide content was depressed at least once below a minimum normal value of 22.5 mM/L. in one brother (W. T.) and in the three youngest children (J. C., L. C., T. C.). The biochemical diagnosis of a mild compensated metabolic acidosis was confirmed in two children (L. C. and T. C.) by analysis of arterialized cutaneous blood for pH and carbon dioxide, and calculated buffer base concentration; pH values lay just below the normal range and the buffer base concentrations were below the minimum normal value of 45 mEq./L.

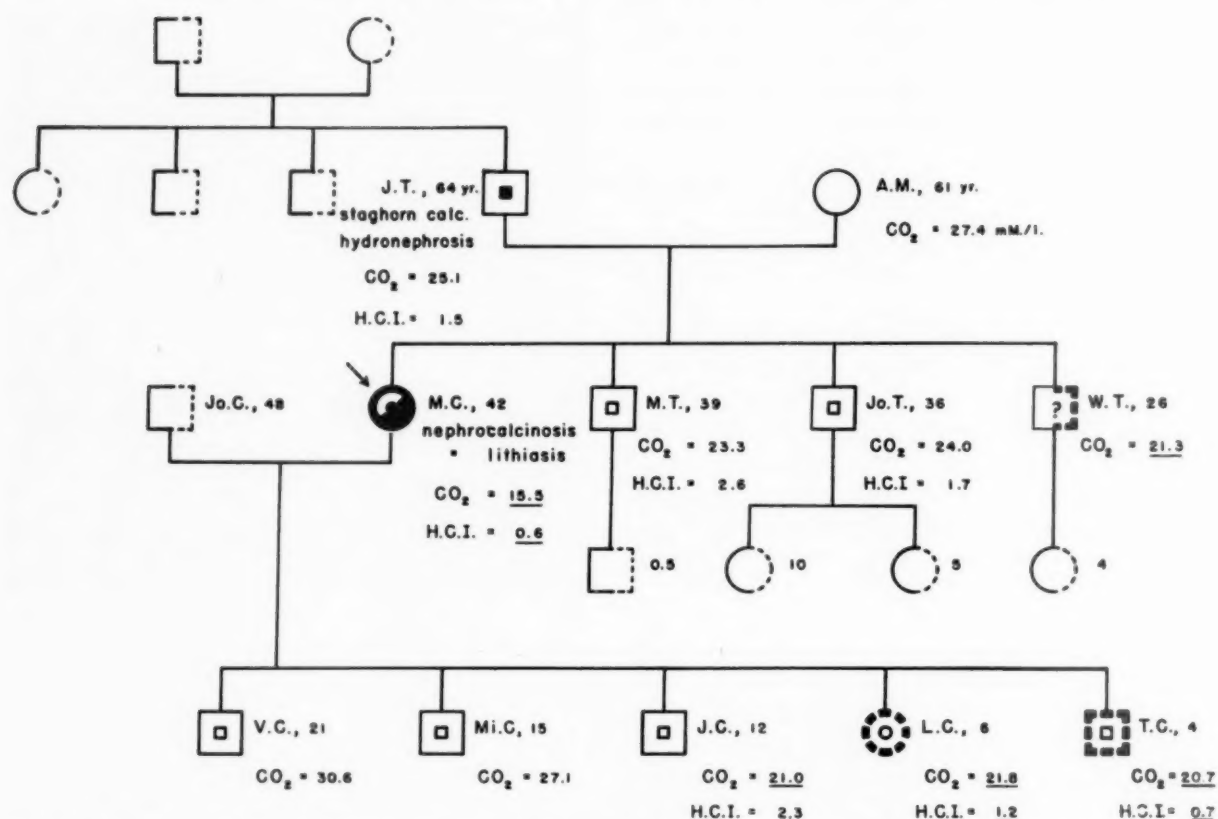


FIG. 2. Family tree of patient (M. C.) with renal tubular acidosis. Symbols indicating clinical, roentgenographic and chemical findings are as defined in Figure 4. Carbon dioxide values are the concentrations in venous serum. "H.C.I." refers to the hydrogen ion "clearance" index as described in the second paper in our series [2]; the minimal normal value being 1.4. Values for carbon dioxide and H.C.I. that revealed abnormalities are underlined. The father of the proposita had staghorn calculi and calcium deposits in one kidney, one brother and three children exhibited low serum levels of carbon dioxide, and two of these children responded abnormally to a test load of ammonium chloride, as shown by the H.C.I.

Ammonium Chloride Loading Test. The father of the patient, her two non-acidotic brothers and her three mildly acidotic children were tested for their ability to excrete acid. As shown in Table 1, the ingestion of ammonium chloride for three days led to a fall in serum carbon dioxide content and to urinary acidification. When the absolute rate of total acid excretion on the third day was related to the reciprocal of the serum carbon dioxide level by the hydrogen ion "clearance" index (H.C.I.), this index was abnormally low in two of the three acidotic children (L. C. and T. C.).* In addition, the analogous indices for titratable acid and ammonium ion excretion show that these two youngest children and their grandfather (with the staghorn calculus) had low indices for titratable acid; in the grandfather, however, the excretion of ammonium was sufficiently high to lead to a normal total hydro-

gen excretion despite the low "clearance" of titratable acid. It is clear, however, that the two children did excrete urines with pH values, when tested with ammonium chloride, appreciably below that usually seen in patients with primary renal tubular acidosis.

Acetazolamide Test. The patient's two youngest children (L. C. and T. C.) who exhibited mild acidosis and a low hydrogen ion "clearance" index, were given a standard dose of the carbonic anhydrase inhibitor, acetazolamide. During the second and third hour after administration the change in bicarbonate excretion was plus 79 and plus 271 $\mu\text{Eq./minute/1.72 M}^2$, respectively, in the two children. The first value for one child (L. C.) was smaller than the minimal values for non-acidotic normal subjects, as presented in the preceding paper [3].

Interpretation of this Family Study. These findings suggest, but do not prove, that a genetic factor is involved in the etiology of renal tubular acidosis in this patient (M. C.). The evidence for subclinical impairment of the ability of the kidney to excrete acid in

* Dr. Lewis A. Barness very kindly observed these two children on the Pediatric Ward of the Hospital of the University of Pennsylvania, where the ammonium chloride studies were conducted. The children were found to be healthy and to have a normal growth for their ages.

TABLE I
ANALYSES OF BLOOD AND URINE BEFORE AND DURING THE ADMINISTRATION OF AMMONIUM CHLORIDE AND HYDROGEN ION
"CLEARANCE" INDICES IN RELATIVES OF PATIENT (M. C.)

Subject*	Date	Venous Serum†			Arterialized Blood‡				Urine§						"Clearance" indices					
		Dose of Ammonium Chloride† (mEq.)	Carbon Dioxide (mEq. per L.)	Chloride (mEq. per L.)	Creatinine (mg. %)	Cell Volume (% cells)	pH	Carbon Dioxide (mM per L.)	Buffer Base¶ (mEq. per L.)	pH	Titratable Acidity (mEq.)	Ammonium (mEq.)	Chloride (mEq.)	PO ₄ (mM)	Creatinine (mg.)	UV Cr $\frac{[Cr]_u}{[Cr]_s}$ (ml. per min.)	UV H ⁺ $\frac{1}{[CO_2]_u}$	UV TA $\frac{1}{[CO_2]_u}$	UV NH ₄ $\frac{1}{[CO_2]_u}$	
J. T. (father), 64 55.1, 166, 1.61	11/7/57	...	25.1	105	1.05	45.8	7.38	21.5	47.5	5.90	25	23	164	22	1135	85	
	11/18	0	24.1	106	1.00	45.8	7.33	12.7	38.5	5.12	40	99	427	44	1175	80	1.5	0.4	1.1	
	11/21	163	14.4	114	1.10	49.4	
A. M. (mother), 61	9/19/56	...	27.4
	7/20/58	...	27.1	103	5.40	47	34	293	34	1999	124	
	1/14/59 1/17	158	23.6 22.3	106 105	1.00 1.00	5.05 5.05	74	112	408	51	1852	115	2.6	1.1	1.6	
Jo. T. (brother), 36 83.5, 173, 1.96	11/29/57	...	24.0	5.80	34	26	173	33	1793	101	
	12/17/58	0	27.1	104	1.10	58.3	7.30	15.0	35.0	5.15	67	88	330	52	1783	100	1.7	1.0	0.7	
	12/20	170	17.9	111	1.10	
W. T. (brother), 26	7/20/58	...	21.3	103	1.26
	9/19/56 9/3/59	...	28.2	103	1.20	5.51
Mi. C. (son), 15	9/19/56 9/3/59	...	27.1 27.4	104	1.20	6.11
	12/16/57 12/20	0	21.0 19.4	105 111	0.72 0.78	43.7 41.9	7.39 7.38	20.6 15.6	46.2 41.0	6.28 5.09	20.6 48.9	27.1 101.2	211 225	29.3 35.8	1044 1040	116 115	...	2.3	0.8	...
J. C. (son), 12 54.0, 154, 1.50	9/3/59	0	22.5	107	0.78	5.20
	11/16/59	150	21.6	109	0.84	4.93	57.5	85.9	363	36.1	1383	120	2.1	0.8	1.3	
	9/19/56	...	22.4	40.5	7.37	18.2	43.0	5.45	21.4	24.4	115	19.6	608	
L. C. (daughter), 6 41.8, 134, 1.22	12/9/57	0	42.1	7.36	16.7	41.8	5.30	26.6	53.1	171	23.0	571	81	1.4	0.5	0.9	
	12/13	91	17.9	108	0.70
	1/27/58	0	21.8	106	...	43.3	7.43	18.3	44.5
	4/25/58	91	17.3	111	0.71	43.7	7.39	12.7	40.0	5.08	18.9	49.1	143	14.4	456	64	1.2	0.3	0.9	
	1/20/60	0	26.6	40.8	7.42	18.7	45.0
T. C. (son), 4 14.4, 98, 0.61	12/13/57	0	39.9	7.37	16.7	41.8
	1/27/58	0	20.7	108	0.45	40.3	7.44	18.6	45.0	6.28	8.3	8.3	36	12.5	306	133	
	1/30	36.4	11.5	108	1.26	44.5	7.34	9.6	35.0	5.30	11.7	19.9	30	9.6	205	32	0.7	0.3	0.4	
15.0, 100, 0.68	4/25/58	0	39.4	7.45	18.7	45.5
	1/20/60	0	24.4
Minimum normal values (2):		...	22.5	7.38	18.6	45.0	1.4	0.6	0.8	...

* Data following subjects' initials indicate respectively: relationship to the probanda (patient M. C.), age in years, weight in kilograms, height in centimeters, and surface area in M².

† 0 = control day.

‡ Specimens of blood for analysis were drawn at the end of the day indicated.

§ Urine data are expressed in units per twenty-four hours ending on the date indicated.

¶ Buffer base concentration calculated according to the method of Singer and Hastings 40).

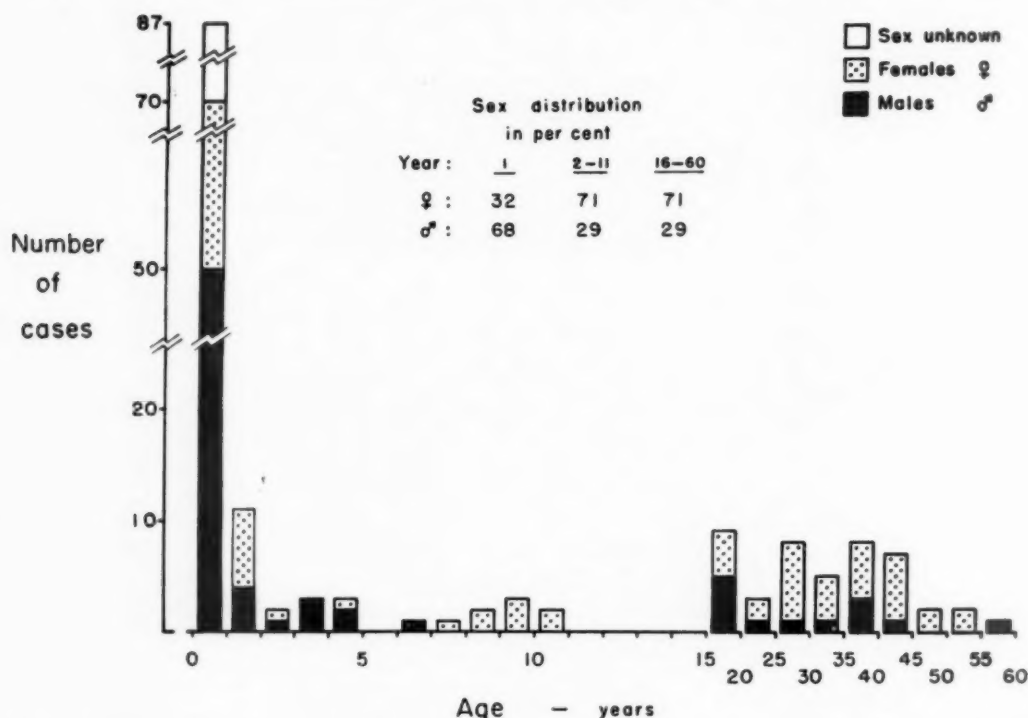


FIG. 3. Age and sex distribution of 162 cases in the literature of primary renal tubular acidosis. In the first year of life the highest incidence of onset of the syndrome occur and the patients are predominantly male; after the first year of life the majority of patients are female.

some of her relatives consists of: (1) low venous serum total carbon dioxide levels and arterial buffer base concentrations in one brother and three of her children; and (2) low hydrogen ion "clearance" indices on acid loading in two of these children. The unilateral staghorn renal calculus in her father and the renal response to the administration of a test dose of acetazolamide in the two children are inconclusive evidence. Even the low hydrogen ion "clearance" indices in the two youngest children must be regarded with some reservation since large correction factors were applied for their small body size and the results judged by adult standards. Conclusive evidence of familial defect awaits further examination of the third mildly acidotic brother (who did not cooperate in this study) and, especially, the development of the younger children. The onset of nephrocalcinosis, as well as more severe acidosis, would be definitive proof that may take a decade or more to appear. Continued observation of this family is in order to be sure of the diagnosis and to evaluate the need for preventive therapy.

COMMENTS

Nosology. Before the data from this family can be interpreted against the background of the previously reported cases, the background itself must be examined. Does the syndrome of renal tubular acidosis represent one disease, excluding

the related disorders mentioned (see Introduction) or several? If it represents several diseases, how can the entities be separated? To examine this background we have reviewed 162 cases of the syndrome, patients with primary renal tubular acidosis uncomplicated by other tubular defects (as in the Fanconi syndrome), reported from 1936 to date.* The evidence from this review suggests that there are at least two disease entities which may be distinguished from each other on the basis of age of onset, sex distribution, incidence of recovery, and family pattern.

If the age distribution of the syndrome is plotted, using the age at which symptoms first appeared, (Fig. 3), a very large group appears in the first year of life; this group is composed of two-thirds males and one-third females. A smaller group appears between one and ten years of age, made up of about 70 per cent females and 30 per cent males. After a gap in the pubertal years, there are additional patients who are affected after the age of sixteen and again this older age group contains predominantly females in a similar ratio.

* The detailed results of this survey and the complete bibliography will appear in a review to be published elsewhere [8].

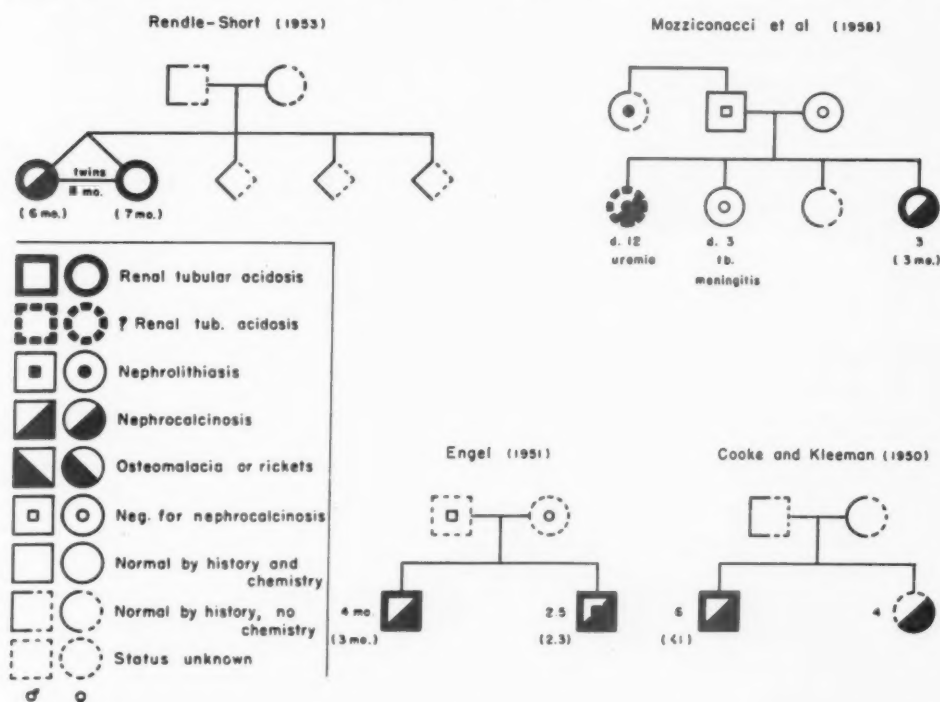


FIG. 4. Infantile primary renal tubular acidosis: families in which manifestations appeared in more than one member, as reported in the literature. Symbols indicating clinical, roentgenographic and chemical findings are defined on the left; squares indicate males, circles females, and diamonds sex unknown. Age of first observation is given in years or months, apparent age of onset is in parentheses. In each of these families there were two siblings with definite or suspected renal tubular acidosis [9-12].

In follow-up studies of patients first involved in the first year of life, a majority recovered clinically and no more alkali therapy was needed. (Table II.) In some of the patients from this group the syndrome might conceivably reappear later in life, but of all the patients with this syndrome who first received medical attention after two years of age, only four had symptoms before the age of one. Of the patients first appearing in the one to ten years of age group, only three recovered and these three were all first affected between the ages of thirteen to eighteen months. None of the patients first showing symptoms after one and a half years of age have been reported to show complete recovery. There may be some overlap between the two groups across the arbitrary dividing line of age of onset before and after one year.

In addition to these features of the syndrome which suggest that the patients may be segregated into an infantile and a late group on the basis of age of onset, sex distribution, and recovery, there is a distinct difference between the two groups in the family histories. For most of the patients with manifestations in the first year

of life there is no evidence of involvement of siblings or parents. However, in four patients from this age group, proved or probable involvement of siblings was found in the families reported by Cooke and Kleeman [9], Engel (Cases 1 and 2 [10]), Rendle-Short (identical

TABLE II
INCIDENCE OF RECOVERY IN PATIENTS WITH PRIMARY
RENAL TUBULAR ACIDOSIS

Age at Onset of Manifestations	Died (%)	Recovered* (%)	Not Recovered* (%)	No. of Patients†
1-12 mo.	14	69	17	83
1-10 yr	20	20	60	15
16-60 yr.	0	0	100	13

* Recovery defined as clinical well being without alkali therapy. Clinical observations on patients of the one to twelve month group have not exceeded a period of thirty-two months. For most patients who have not recovered, this period was less than one year.

† Includes only patients for whom our estimate of recovery can be made from the data reported.

TABLE III
SIBSHIP INCIDENCE OF INFANTILE PRIMARY RENAL
TUBULAR ACIDOSIS

Data	Number of Sibships	Total Number of Sibs	Affected Sibs*
All sibships	19	49	23 (47%)
Sibships 4 or larger	5	24	7 (29%)

NOTE: Number of sibships with sex of all sibs identified is too small for analysis of sex ratio.

* Percentage of involvement is in parentheses.

twins) [17], and Mozziconacci *et al.* [12]. (Fig. 4.) But in none of these families was there evidence of involvement of the parents. The youngest patient with evidence of the syndrome in a parent was the girl described by Foss *et al.* (Case 3 [13]), who first showed presumed manifestations at one and a half years of age; her father had renal stones and a "low carbon dioxide value" in plasma. Therefore, if the syndrome in patients appearing with symptoms in the first year has any genetic basis at all, it would be that of a recessive gene. An analysis of the incidence of the infantile form of the disease in sibships recorded in the literature (Table III) shows that 23 sibs of 49 in 19 sibships were affected, or 47 per cent, clearly higher than that of 25 per cent expected from a recessive gene. But in four of these sibships there was only one sib; and in nine, only two. In five sibships with four or more sibs,* the incidence of affected persons was seven of 24, or 29 per cent. This incidence is clearly compatible with that attributed to a recessive gene. Further data in favor of a recessive gene are two marriages of first cousins in the case reports of Rendle-Short [17] and of Jurow and Worthen [14], a minimum of 2.6 per cent in eighty-five families (history bearing on consanguinity was not given in all case reports). In contrast, the genetic data from patients appearing after the first year, to be discussed subsequently, suggest that in the older patients the syndrome may represent a disease due to a dominant gene with varying "penetrance" and "expressivity."

These aspects of the syndrome suggest that the

* The lowest incidence that could be described in sibships of one or two sibs taken from case reports of affected persons would be 50 per cent. Hence to expect to find evidence for a recessive gene in this analysis, one must use only larger sibships.

patients may be divided into two groups. The first group of patients, whom we label infantile primary renal tubular acidosis, shows manifestations in the first year of life, contains two-thirds males* exhibits an apparently high recovery rate, and manifests very little obvious familial involvement (in only a very few instances, siblings are affected and parents are not affected at all). The principal etiology of this group may well lie in a delay in maturation of renal function due to a recessive gene or some non-genetic cause. The second group of patients, whom we label late primary renal tubular acidosis, first show manifestations after the first year of life; two-thirds of this group are females; the group has a low rate of recovery, and in the families of this group of patients in more than one generation some manifestations of the syndrome are shown. The rest of the discussion will proceed to further analysis of the available family data for the late group and to consider possible biochemical disturbances which may produce the disease.

Genetics. Family data, positive or negative, have been reported for twenty-one patients with late primary renal tubular acidosis, including the C. family reported on herein. In some of the reports the data on members other than the proband are limited to a history of no involvement with the syndrome or with possibly related disorders, but at least the members are identified as to relation to the proband. In thirteen of these families there was no evidence of involvement among two to eight siblings or in the parents. However, in some of these families the negative evidence is limited by the fact that there is no history of an appropriate disorder, nephrocalcinosis was not excluded by roentgenographic examination, and metabolic acidosis was not excluded by chemical studies.

A group of eight families remains (see Figures 2 and 5; C. family and families reported on by other investigators [5,13,15-18]) in which the proband first had symptoms of the disease after the age of one year and at least one blood relative had metabolic acidosis, nephrocalcinosis or nephrolithiasis, or some combination of these findings. Despite the fact that some or all of these manifestations have not been confirmed or

* The number of sibships with sex identification reported for the infantile group was too small to determine whether or not the high male to female ratio in reported cases was due to a preponderance of males in total sibships.

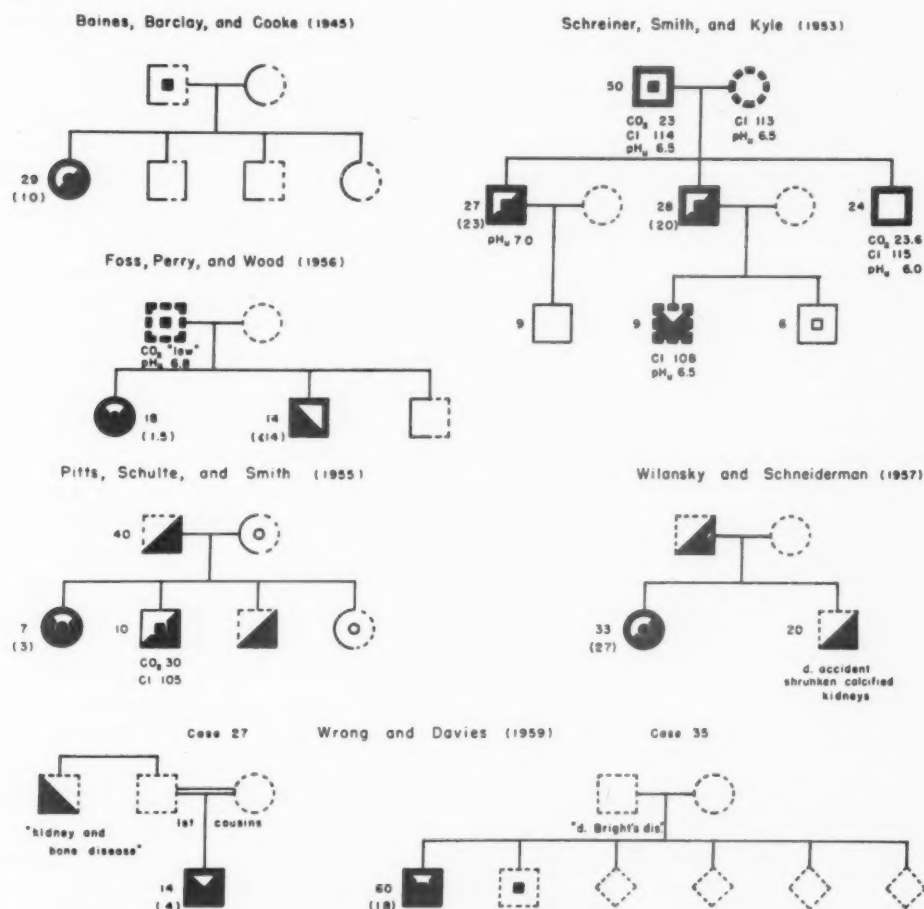


FIG. 5. Late primary renal tubular acidosis: families in which manifestations appeared in more than one member, as reported in the literature. Symbols are as defined in Figure 4. Involvement of more than one sibling, and of parents, is notable [5,13,15-18].

excluded in all relatives, at least one parent shows a manifestation in six families (C. family and five others [5,13,15-17]). In the family of Schreiner, Smith and Kyle [15], the father probably had hyperchloremic acidosis, in addition to nephrolithiasis; the same interpretation is less certain in the family of Foss, Perry and Wood [13]. Two relatives, the father in the C. family and a brother in the family of Pitts, Schulte and Smith [16], have had calcium deposition as calcinosis or lithiasis with acidosis apparently excluded. In the other relatives with at least one manifestation, acidosis was not proven or excluded. Of the eight families, in two (C. family and family of Schreiner *et al.* [15]) there is evidence that a third generation may be involved.*

* A personal communication from Dr. Russell E. Randall, Jr. indicates that a further study of the family originally reported by Pitts *et al.* [16] has revealed overt renal tubular acidosis in two siblings, the father, an aunt and a daughter, and grandmother of the proposita.

An analysis of the incidence of affected persons in ten sibships (Table IV) shows that sixteen of thirty-nine sibs, or 41 per cent, have at least one manifestation of primary renal tubular acidosis. This incidence, as well as the incidence by sexes, is not significantly different from a 50 per cent incidence predicted for a dominant gene. It must be conceded that the apparent incidence in sibships may be excessively high due to a bias inherent in the reporting of full sibship composition largely for patients in whom relatives were found to have some manifestation. Unfortunately, in most of the case reports, there is no evidence of investigation of siblings.

With this evidence at hand a genetic hypothesis may be set up to account for the characteristics of the late group. A dominant gene will account for the appearance of the syndrome in at least two to three consecutive generations and for an incidence in sibships not significantly different from 50 per cent. The gene will have fullest

TABLE IV
INCIDENCE OF LATE PRIMARY RENAL TUBULAR ACIDOSIS
IN TEN SIBSHIPS

Sex	Number of Sibs	Affected Sibs	Affected (%)	Sex Distribution in Affected Sibs (%)
Male	20	7	35	44
Female	19	9	47	56
Total	39	16	41	100

NOTE: Ratio of males to females in sibships is not significantly different from 1:1 (by Chi-square test). Observed incidence of total affected sibs and of affected male sibs is not significantly different from a theoretical 50%. Sex ratio of affected persons in the entire late group (Fig. 3) is significantly different from that predicted by the observed distribution in sibships of known composition shown in this table ($p < 0.02$).

expressivity in females (relatively lower in males); which will account for the over-all preponderance of females in the entire late group, for a higher female incidence in the sibships analyzed (Table IV), and for the appearance of the syndrome without apparent acidosis in males* (the father of Mrs. C. and brother in family of Pitts, Schulte and Smith [16]). The disease might restrict fertility of females either biologically or socially and thus account for a preponderant involvement of fathers in the families reported. The data available are clearly inadequate for a multigenic hypothesis. It must be admitted that some sporadic cases in the late group may be secondary to a primary pyelonephritis, but at the present time there is no certain way to be sure which cases these might be.

So far, a comparable disease picture with a genetic basis has not been described, to our knowledge, in other animals, but the genetically determined differences in blood pH among two strains of inbred mice [19] may prove to be an exception.

Pathogenesis. That the disease of late primary renal tubular acidosis is genetically determined in at least a portion of the cases seems probable.

* It should be noted that the three patients reported on by Wrong and Davies [18] as having "incomplete renal tubular acidosis" (overt acidosis prevented by an increased ammonium excretion despite a defective response of urinary titratable acid to an ammonium chloride load), were all males.

That the disease should be due to an enzymatic defect so determined, seems very likely. After the metabolic effects of the administration of acetazolamide (metabolic acidosis, production of alkaline urine, induction of nephrocalcinosis [20]) were demonstrated to be linked to the inhibition of carbonic anhydrase activity in the kidney, a deficiency of this enzyme in the kidneys of patients with renal tubular acidosis seemed to be a logical hypothesis to explain their chemical derangements. But so far, such a deficiency has not been proven in this group of patients; indeed Yaffe, Craig and Fellers [27] have found normal carbonic anhydrase activity in a renal biopsy specimen obtained from a four year old girl with the syndrome of primary renal tubular acidosis. When our patients were given acetazolamide [3] they immediately excreted a much more alkaline urine; but when their response was quantitatively measured and found to be less than in normal subjects, the smaller response appeared to be due to lower concentrations of filtered serum bicarbonate and to be no less than that seen in normal persons made acidotic with the administration of ammonium chloride. Thus, although the findings in our study might be compatible with a carbonic anhydrase deficiency in late primary renal tubular acidosis, they do not prove it.

Positive clues to other enzymatic defects in this disease are very few. Berliner, Kennedy and Hilton [22] and Harrison and Harrison [23] have induced a temporary syndrome of metabolic acidosis, excretion of alkaline urine, hyperphosphaturia and hyperaminoaciduria in rats by injections of maleic acid, which is known to inhibit *in vitro* enzymes containing sulfhydryl groups, notably succinic dehydrogenase in the Krebs cycle [24]; but this experimental syndrome resembles the Fanconi type and is unlike renal tubular acidosis in that multiple functional defects of the renal tubule are produced. Yaffe, Craig and Fellers have reported that activity of triphosphopyridine nucleotide diaphorase, linked to isocitric dehydrogenase in the tricarboxylic acid cycle, was deficient in the renal biopsy specimen obtained from their four year old patient with renal tubular acidosis. Both of these experimental observations suggested that impairment of hydrogen secretion against a concentration gradient might be due to defective energy supply from the Krebs cycle in the tubular cell rather than to a specific defect in enzymes responsible for hydrogen ion secretion.

The appearance of nephrolithiasis and nephrocalcinosis in this disease has been attributed to the associated hypercalciuria [6]. However, defective renal production and urinary excretion of citrate in the presence of metabolic acidosis [20,25] and consequent loss of the calcium-chelating effect of citrate is an engaging alternative explanation. Indeed, the demonstration that citrate excretion is greater in the presence of estrogenic hormones and less in the presence of androgenic hormones [26] suggests that females, perhaps adapted to or requiring normally a higher rate of citrate formation, may be more sensitive to the consequence of inhibition of citrate formation by acidosis, and may offer an explanation for the preponderance of female cases in the late group. Alternatively, it is possible that defective renal citrate formation is the underlying disorder in this disease and that acid formation may or may not be impaired as a consequence.* In favor of such a view is the finding in the C. family of a father with a staghorn calculus but without an impaired response to ammonium chloride test load and, in the family reported on by Pitts *et al.*, the brother with nephrolithiasis but without apparent acidosis. However, at present, there is no direct evidence to show that defective citrate formation causes impairment of acid excretion.

Despite the great probability that the group of patients whom we have labeled as late primary renal tubular acidosis represents one disease entity, there may be in this group patients in whom the syndrome has not developed from a genetic defect but who have acquired the syndrome from other possible causes. Pyelonephritis undoubtedly may be secondary to renal tubular acidosis, especially with nephrocalcinosis and nephrolithiasis. Can it be a primary cause? Renal tubular acidosis is rare and pyelonephritis is common. Damage to the renal tubule secondary to pyelonephritis was the cause ascribed by Albright and his colleagues [6] to the early cases which they reported in their monograph. The basis for this conclusion was the frequency of pyelonephritis in those patients. Data on the positivity or negativity of urine culture is available for thirty-three patients in the older

group, eleven males and twenty-two females. Positive cultures turned up in four of eleven males and twelve of twenty-two females, but we believe that as low an incidence as this suggests that pyelonephritis is not the etiologic factor for most of the late group; the infection, when present, could as well be a secondary manifestation of nephrolithiasis or potassium depletion.

In Figure 3 the sex distribution of reported cases in the late group is seen to be 29 per cent males and 71 per cent females. The reported data are insufficient to decide whether or not this sex ratio is a consequence of a possible preponderance of female sibs in sibships of all reported cases. In the sibships, analyzed in Table IV, the sex ratio of affected persons is 44 per cent males and 56 per cent females. The higher ratio in the entire group is significantly different, by the Chi-square test, from that found in the ten analyzed sibships and is in favor of higher expressivity of a dominant gene in females or of pyelonephritis (a disease with a much higher incidence in females in general) as an etiologic factor for sporadic female cases in the late group. Latham [28] has reported on a small group of patients in whom renal hyperchloremic acidosis was evidently a sequel to pyelonephritis. These patients are not included in the groups discussed herein because of the uncertain extent of generalized nephron damage, the excretion of markedly acid urines, and the presence of hyperkalemia.

Can hypercalcemia, hypercalciuria or nephrocalcinosis due to causes other than the defect in renal tubular acidosis selectively impair renal excretion of acid? In one of our patients (M. D., reported on separately [29]), renal tubular acidosis and nephrocalcinosis developed after the onset of hyperthyroidism. Since the hyperthyroid state is known to lead to the mobilization of skeletal calcium [30], a high rate of excretion of calcium, and consequent tubular damage, might have been a factor in the development of tubular acidosis in this patient. Fourman, McConkey and Smith [31] have reported evidence of impaired acid excretion in primary hyperparathyroidism; Thomas, Connor and Morgan [32] have pointed out that although hypercalcemia of various origins may be accompanied by small rises in serum total carbon dioxide, the hypercalcemia of hyperparathyroidism is more likely to be accompanied by small reductions in venous total carbon dioxide. Much remains to be learned of the interrelation-

* A patient reported by Bauld, MacDonald and Hill [27] excreted half the minimal normal amount of urinary citrate even while on alkali therapy, but the data are insufficient to decide what portion of her renal tissue was functioning. (See "Addendum.")

ship between renal calcification and acid excretion.

Potassium depletion may be a result of renal tubular acidosis; can it be a cause? The clinical observations of Relman and Schwartz [33] and the experimental work of Hollander, Oliver and colleagues [34,35] have shown that potassium depletion in the rat produces a characteristic morphologic lesion in the collecting ducts. These are tubular loci in which urinary acidification and water reabsorption take place [36,37], and defects in the two functions of water reabsorption and acid secretion are often associated in renal tubular acidosis. However, although experimental potassium depletion appears to lead to some impairment of maximal lowering of urine pH [38], there has been no clear demonstration that following recovery from depletion a permanent impairment of acid excretion remains. Perhaps the two siblings with renal tubular acidosis and nephrocalcinosis reported on by Cooke and Kleeman [9] acquired their tubular lesions as the result of congenitally determined pylorospasm, vomiting, alkalosis and potassium depletion. This sequence is rendered unlikely by the complete absence of nephrocalcinosis or acidosis in a group of fifty such children with pylorospasm in a follow-up study by Cooke and Lancaster [39].

Conclusion. Better clarification of the nosology of this syndrome will be reached in at least three ways. First, longer follow-up study of patients from the infantile group and their parents is needed. The apparently high recovery rate in this group may be spurious, due to excessively short periods of observation and insufficient clinical criteria of recovery. None of the parents of infantile patients have been reported to show evidence of the syndrome, but as most of them were probably below thirty years of age when their affected children were seen, the syndrome could go on to develop in later years, as might be deduced from Figure 3.

Second, in most of the studies of the syndrome, exclusion of the disease in siblings or other relatives has been based solely on negative histories; roentgenographic examinations for nephrocalcinosis and clinical studies of blood acid-base values and of renal responses to acid loads (ammonium chloride test) might have been obtained more often. We strongly urge that all investigators of patients with this syndrome make every effort to obtain the evidence, positive or negative, that bears on a genetic etiology.

Manifestations in every member of the patient's family should be sought for by every means: clinical, radiological, physiological and biochemical. The number and sex of the total sibship should always be noted. Only when a great deal more data are obtained and analyzed will the genetic pattern and its etiological role be clarified.

Third, and most important of the needed information, is identification of the underlying biochemical defect or defects in this disorder, probably enzymatic ones. Only then may it be possible to identify the disease or diseases unequivocally, and the clinician will no longer need to rely solely on the secondary manifestations of metabolic acidosis, nephrocalcinosis and lithiasis, and metabolic bone disease, all highly variable expressions, for his diagnosis.

SUMMARY

We have presented herein a study of the family of one patient with primary renal tubular acidosis associated with nephrocalcinosis and nephrolithiasis. A genetic factor in the disease in this patient is suggested by the following observations. The patient's father had unilateral nephrocalcinosis, staghorn calculus and hydronephrosis; one brother and three children were found to have mild depression of the serum carbon dioxide level but no other clinical signs or symptoms. Two of these three children were found to show a low or borderline hydrogen ion "clearance" index when loaded with ammonium chloride. The study illustrates the possibility of detecting latent impairment of the ability of the kidney to excrete acid by use of a standardized provocative test assessed by careful criteria.

We have reviewed and analyzed 162 cases in the literature of primary renal tubular acidosis, excluding certain syndromes with multifactorial defects (e.g. the Fanconi syndrome, Lowe's syndrome, and some secondary types). The 162 cases appear to fall into at least two disease groups: (1) infantile primary renal tubular acidosis with appearance in the first year of life, a high rate of recovery, and a preponderance of males involved; and (2) late primary renal tubular acidosis appearing after the first year of life and through adult life, showing a low recovery rate and a preponderance of females involved.

The disease in the infantile group may be due to a recessive gene or a delay in maturation of

renal function due to some other cause; in the late group, the disease may be due to an autosomal dominant gene with fuller expressivity and penetrance in females.

Although the underlying biochemical disorder in the disease is not known, some inconclusive data are cited to suggest that it may be in the Krebs citric acid cycle.

Some patients in the late group may have acquired the syndrome from pyelonephritis or renal calcific damage of other origins, but the evidence on this question is scanty.

Acknowledgment: We are grateful for the criticisms of our colleagues in the Chemical Section of the Department of Medicine of the University of Pennsylvania and especially for the advice on the genetic analysis from Dr. R. W. Winters.

ADDENDUM

In six patients with renal tubular acidosis, the urinary citrate, related to urine PH, was definitely depressed as compared to that in five normal male subjects and was not returned to normal by alkali therapy given for periods of three to nine years (DEDMON, R. E. and WRONG, O. Citrate excretion in renal tubular acidosis, in preparation).

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598 Hydrogen Ion Excretion in Renal Tubular Acidosis. III—Huth et al.

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Idiopathic Paroxysmal Myoglobinuria*

Report of Two Cases Occurring in Sisters Review of the Literature

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MYOGLOBIN may appear in the urine as a result of crush injuries [1], electric shock [2], § beatings [3], burns [4], arterial thrombosis [5] and ingestion of alcohol with or without sedatives [6-8]. An epidemic form of myoglobinuria, Haff disease, which seems to be of infectious or toxic etiology, has been described outside the United States [9]. There are, in addition, cases of spontaneous myoglobinuria both associated [7,10-16] and not associated [4,17-34] with a classifiable type of muscular disease. These cases present a rather typical clinical picture, variously called idiopathic paroxysmal myoglobinuria, acute recurrent rhabdomyolysis [4] and paroxysmal paralytic myoglobinuria. This syndrome resembles the condition, equine myoglobinuria, seen in work horses [39]. The cases to be described are of the idiopathic type and fall into the small group in which there is a familial occurrence [4,7,35,37].

Table I summarizes all relevant cases found in the literature. Those associated with known trauma have not been included except for the interesting case reported by deLangen [3].

CASE REPORTS

CASE I. M. T. (U. V. H. 196289), a sixteen year old white unmarried girl, was born in the University of Virginia Hospital on November 9, 1943, following an uncomplicated pregnancy. She was noted to be a healthy infant. At the age of four she was seen in the Pediatric Clinic because of pain in the abdomen, shoulder and legs associated with vomiting. No abnormal physical findings were noted and no laboratory data were obtained. She was seen again in the clinic three years later at which time she was treated for pneumonitis; she was well otherwise.

Her first admission to the hospital was to the

§ Quoted in reference 4.

surgical service at the age of nine for appendectomy. The complaints then were cramping, lower abdominal pain of forty-eight hours' duration, anorexia, vomiting, fever and sore throat. It was stated that she was "unable to walk" but no further details were given. Physical examination revealed a temperature of 103.4°F., pulse 120 per minute, respirations 24 per minute and blood pressure of 118/72 mm. Hg. She was found to have an exudative tonsillitis and moderately severe, generalized abdominal tenderness most marked in the right lower quadrant. No abnormalities were described on neurological examination. The urine was clear yellow and except for a specific gravity of 1.007 was normal. Hemoglobin was 13.5 gm. per cent and a white blood cell count was 15,600 per cu. mm. with 87 per cent granulocytes. The appendectomy was uncomplicated and the pathology report was "early acute appendicitis." The patient became afebrile on the day after surgery and was asymptomatic when discharged on the fifth hospital day.

When next seen in the Pediatric Clinic on January 27, 1957, at the age of thirteen, she had a one day history of pain in the neck, abdomen and extremities without associated weakness. The urine output had been scanty for two to three days but dark color was not noted. The positive physical findings were spasm of neck muscles, diffuse abdominal tenderness, pain in thighs on raising legs straight, bilateral flank tenderness and hypoactive deep tendon reflexes. The white blood cell count was 24,000 per cu. mm. and a urine specimen obtained by catheter contained 2-plus albumin and clumps of white blood cells. The diagnoses then were torticollis and acute pyelonephritis. After treatment with acetyl sulfisoxazole for ten days the urine cleared and the patient apparently recovered completely.

Her next admission was to the Obstetrical Service in April 1958 at which time she gave birth to a healthy female infant. Except for a mild elevation of blood pressure antepartum, the pregnancy and delivery were uncomplicated.

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TABLE I
REPORTED CASES OF IDIOPATHIC PAROXYSMAL MYOGLOBINURIA

Author	Age (yr.) and Sex	Clinical Data	Myoglobin Demonstrated	Muscle Biopsy	Comment
Paul [77]* 1923	42, F	Acute episode of severe generalized muscle pain associated with fever and dark red urine; died 2 weeks later with bronchopneumonia	Oxyhemoglobin and methemoglobin (spectroscopic)	Autopsy, waxy degeneration of muscle	Thought by others to be dermatomyositis [38]
Gunther [78]* 1924	54, M	Recurrent fever with muscle weakness and joint swelling associated with dark urine; death due to pneumonia and cellulitis	Methemoglobin (spectroscopic)	Autopsy, "fish flesh" appearance of muscle tissue; degenerative, inflammatory and necrotic	Atypical case thought by others to be dermatomyositis [38]
Debré et al. [79]* 1934	6, F	Recurrent attack of generalized muscle spasm associated with fever and dark urine	No	No	
Huber et al. [20]* 1938	4, M	Muscle pain, weakness and spasm of legs, associated with dark urine and fever; single episode precipitated by walking; complete recovery in one month	No	No	
Millikan [27] 1939	Adult, M	Clinical picture similar to equine myoglobinuria; no further details	Spectroscopic	No	Rise in plasma K ⁺ during exercise
Bywaters, Dible [22] 1943	24, M	Since childhood recurrent bouts of muscle stiffness following exercise; in adolescence these were associated with "black urine"; last such attack associated with streptococcal pharyngitis, acute renal failure and death	No	Autopsy, scattered hyaline necrosis; patchy fragmentation and loss of eosin staining	Kidneys showed acute tubular necrosis with no evidence of glomerulonephritis
Buchanan, Steiner [23] 1951	4, M	At age 2½ years transient weakness developed of left extremities associated with "bloody urine"; last episode followed violent exercise and was characterized by progressive complete muscular paralysis including deglutition muscles; death occurred despite use of respirator	Spectroscopic	Autopsy, waxy degeneration, vacuolization and necrosis	
Hörmon [24]* 1954	64, M	Single episode of severe left calf and thigh, muscular tenderness associated with dark urine; anuria and uremia reversed after 10 days; patient later died of cerebral thrombosis	Spectroscopic	Autopsy, degenerative foci with loss of striation and sarcolemmal proliferation	Kidneys showed "distal tubular nephrosis"
Spaet et al. [25] 1954	23, M	Lifelong history of muscle cramping with exertion; cortisone administration followed by prescribed exercise produced a severe episode of muscle pain and myoglobinuria lasting 12 hours; the following day anuria developed and lasted 14 days requiring hemodialysis	Spectrophotometric	Minimal non-specific changes during attack	Bilirubin slightly elevated
Fletcher, Prankerd [26] 1955	21, M	Attack of myoglobinuria produced by cold and exertion; no further clinical data	Electrophoretic		
Schaar [27] 1955	9, M	Two days after respiratory infection and strenuous work, an episode of fever, headache and meningeal signs associated with dark urine; recovered over 2½ week period; one subsequent attack of muscle stiffness 4 months later	Spectroscopic	Areas of degeneration	Increased creatine excretion during attack; normal glucose tolerance
Berenbaum et al. [28] 1955	10, F	Appendectomy for abdominal pain followed by attack of muscle pain and tenderness with dark urine of 4 days' duration; history of muscle cramps and dark urine at age 4	Spectrophotometric	Waxy degeneration and fragmentation	Normal glucose tolerance curve; renal glycosuria
Reiner et al. [29] 1956 Case 1	46, M	Since childhood, recurrent attacks of severe muscle weakness and pain, precipitated by exercise; reported attack of pain in thighs and reddish brown urine was complicated by oliguria requiring 4 days of peritoneal lavage with recovery	No	Segmental, widespread muscle necrosis	Patient had hypertension and old cerebral vascular accident
Case 2	42, M	Since age 19 five episodes characterized by loss of consciousness, muscle tightness, weakness and dark urine; reported episode was complicated by anuria with recovery	No	Segmental, widespread muscle necrosis	Flat glucose tolerance curve

NOTE: See footnotes on page 603.

TABLE 1 (Continued)
REPORTED CASES OF IDIOPATHIC PAROXYSMAL MYOGLOBINURIA

Author	Age (yr.) and Sex	Clinical Data	Myoglobin Demonstrated	Muscle Biopsy	Comment
Bowden et al. [4] 1956 Case 2	8, F	Following tonsillectomy onset of muscle pain and tenderness associated with dark urine; unable to move for 2 days but recovered except for residual foot drop; 2 previous episodes both with associated fever, 1 complicated by anuria of 7 days' duration	Spectrophotometric	No	Increased creatine, decreased creatinine excretion during attack
Case 3	6, M	Episode of muscular pain of increasing severity followed by periorbital edema and dark urine; muscle weakness present for 2 weeks with complete recovery	Spectroscopic	No	Increased creatine, decreased creatinine excretion during attack; elevated 17-ketosteroid excretion
Pearson et al. [37] 1957	57, M	Onset, age 20, of frequent episodes of calf pain following exercise; dark urine noted with more recent attacks; exercise precipitated episode complicated by anuria for 13 days with recovery	Spectrophotometric	Normal during remission	Patient has diabetes mellitus; after attack total exchangeable K ⁺ fell and Na ⁺ rose
Berg [32] 1958	22, M	Since age 20, several attacks of mild low back pain associated with dark red urine and fever; 4 to 6 hours after induced fever, muscle aching and myoglobinuria occurred; episodes not precipitated by exertion	Spectrophotometric	Normal between episodes	
Segar [33] 1959	15, M	Frequent episodes of pain in lower extremities following exertion; present episode characterized by fever, chills and severe respiratory distress; muscles were swollen, firm and tender; respirator used 18 days, severe oliguria and uremia required intraperitoneal and artificial kidney dialysis; complete recovery	Spectrophotometric	No	
Gillett [34] 1959	19, M	Single episode of severe, painful, swollen tender muscles of upper extremities and trunk associated with reddish brown urine following forced calisthenics; the forced exercise followed a 2 week rest after daily weight lifting for 2 years; oliguria of 4 days' duration noted; urine dark for 1 week	No	Non-specifically abnormal	Elevated creatine excretion following the attack
Whisnant et al. [30,58]† 1959	24, F	Myalgia, weakness, dark urine for 3 days; no previous episode or association with exertion; had mild fever but no demonstrable muscle weakness; potassium intoxication necessitated peritoneal dialysis; diuresed on 14th hospital day; has had recurrent red urine	Electrophoresis and ultracentrifuge	No	Had hemoglobinemias and hemoglobinuria in addition; renal biopsy revealed acute tubular necrosis
WRAH‡ 1959	49, M	One severe attack characterized by pain and tenderness of extremities and dark urine; oliguria for 6 weeks necessitating 4 dialyses on artificial kidney; gradual, slow, recovery complicated by bilateral foot drop; history suggestive of previous attack but no relationship with exertion	Electrophoresis of urine and serum	No	
Javid et al. [60] 1959	18, M	Recurrent attacks of muscle pain, weakness, and dark urine following exertion	Spectrophotometric and electrophoresis of urine and serum	Normal 48 hours after onset	
Daugherty et al. [67] 1959	26, M	A single attack following unusual exertion; muscle cramps, pain, weakness and dark urine; recovery in 3 days	No; benzidine-positive urine	No	

Idiopathic Paroxysmal with Familial Occurrence

Hittmair [35]¶ 1925	43, F	For 2 years, recurrent episodes of severe muscle pain and weakness associated with dark urine and related to exertion; complete recovery in 2 weeks after each episode	Oxyhemoglobin and methemoglobin (spectroscopically)	No	Brother had similar attack
Schaar et al. [36] 1949	23, M	Fatal case with death due to pulmonary edema and renal insufficiency	Spectroscopic	Autopsy, significant but undescribed muscle changes	Kidneys showed hydropic degeneration of proximal convoluted tubules; family history suggestive but no details given

TABLE I (Continued)
REPORTED CASES OF IDIOPATHIC PAROXYSMAL MYOGLOBINURIA

Author	Age (yr.) and Sex	Clinical Data	Myoglobin Demonstrated	Muscle Biopsy	Comment
Hed [7]† 1955 Case 1	30, M	Since age 14 recurrent episodes of muscle aching and tenderness associated with dark urine after strenuous exertion; more likely to occur in presence of acute infection or when fasting; thyroidectomy, age 25 for thyrotoxicosis	Spectroscopic	Minimal, non-specific, 2 weeks after attack	Diabetic glucose tolerance test; muscle pain without myoglobinuria on low carbohydrate diet; see Hed Case 3 for family history
Case 2	28, M	Onset age 18 of frequent muscle pain and weakness associated with dark urine following exercise; thyroidectomy age 24 for non-toxic goiter	Spectroscopic	No	Severe attack followed 57 hour low carbohydrate diet; see Hed Case 3 for family history
Case 3	35, M	Onset age 20, attack identical to Case 2; isosthenuria for 6 weeks after attack at age 22	Spectroscopic	No abnormality 2 days after attack	Glucose tolerance curve slightly suggestive of diabetes; attack followed 48 hour low carbohydrate diet and 100 meter walk; increased creatine excretion during attack and on low carbohydrate diet; Hed's cases 1, 2 and 3 are brothers in sibship of six; 2 brothers and 1 sister are normal, mother has diabetes
Bowden et al. [4] 1956 Case 1	4, M	Lumbar pain, fever and dark urine associated with shigella infection; had had three similar previous episodes; 4 months after reported episode he had muscle soreness and sudden death	Methemoglobin (spectroscopic)	Autopsy, severe acute muscle damage	Sister had muscle pain and dark urine (Bowden Case 4)
Case 4	4, F	Onset at age 3 years of pain and weakness of the legs associated with dark urine; sudden death at age 4 during a short episode	Spectroscopic	Autopsy, muscle changes as in Bowden Case 1	Sister of Bowden's patient (Case 1)
Fitz [37] 1957	34, M	Episode of generalized muscle tenderness and weakness preceded by 3 days of malaise, aching and rhinorrhea; urine was bright red but later port urine in color, contained no red blood cells or porphyrins; treated with ACTH and vitamin B ₁₂ ; had had similar attack of pain 15 years previously	No	No	Probable case but data incomplete; brother and sister died with illnesses with few features suggestive of myoglobinuria; inadequate information for definite acceptance
Current report Case I	16, F	See text, Case I	Spectrophotometric and electrophoretic	No	Sister is patient in Case II
Current report Case II	15, F	See text, Case II	Electrophoretic	No	Sister is patient in Case I; see family history

Associated with Classifiable Muscle Disease

Meyer-Betz [70]* 1910	13, M	Since age 7 recurrent episodes of muscular weakness associated with dark urine; atrophy of shoulder muscles and pseudohypertrophy of calf muscles present	Oxyhemoglobin, methemoglobin (spectroscopic)	No	Pseudohypertrophic muscular dystrophy
Louw, Nielsen [77] 1944	10, M	Since age 4 reported attacks of muscle pain and difficulty in walking occasionally associated with "bloody urine"; muscles thick and tender; calf muscles prominent	Spectroscopic	No	Pseudohypertrophic muscular dystrophy; 8 cases of progressive muscular dystrophy in family; creatinuria during attack
Sherwin [72]* 1945	38, M	Recurrent muscle pain and dark urine for 4 to 5 years; muscular atrophy developed after the attacks	No	No	Suggestive of muscular dystrophy
Wissler [73]* 1948	6, M	Single attack following exercise characterized by calf pain and dark urine; trunk and arm weakness followed; residual rigidity of calf muscles	Spectroscopic	No	Pseudohypertrophic muscular dystrophy developed; 3 maternal uncles had a form of muscle wasting

TABLE I (Continued)
REPORTED CASES OF IDIOPATHIC PAROXYSMAL MYOGLOBINURIA

Author	Age (yr.) and Sex	Clinical Data	Myoglobin Demonstrated	Muscle Biopsy	Comment
Kreutzer et al. [74] 1948**	39, M	Since childhood, muscle pain, weakness and dark urine have followed mild exertion; patient was studied during precipitated attack; muscle wasting	Spectrophotometric	No	Elevated serum creatinine and creatine during attack; diagnosed as progressive muscular dystrophy
Acheson, McAlpine [75] 1953	30, M	Since age 8 unable to run because of leg stiffness; dark urine first noted at age 22 following skiing and has recurred frequently; changes of muscular dystrophy	No	Occasional atrophic fiber, otherwise normal	Case of muscular dystrophy; sister has pseudohypertrophic muscular dystrophy; serum K ⁺ low before induced attack; 17-ketosteroids elevated
Hed [7] 1955 Case 6	13, M	Onset of muscle weakness at age 2; reported episode of calf aching and tenderness with dark urine after strenuous walking; pseudohypertrophy of calf muscles noted	Spectroscopic	Slight degeneration with edema and inflammation	Pseudohypertrophic muscular dystrophy
Hipp et al. [76] 1955	31, M	Since age 21, difficulty with muscle relaxation after sustained contractions; following electroshock therapy, generalized muscle soreness and swelling with dark urine; an episode later precipitated by exercise	Spectrophotometric	None	Symptoms of myotonia congenita; reactive depressive
<i>Associated with Unusual Circumstances</i>					
deLangen [3] 1946	37, M	Following forced genuflexions and beating with a rifle butt, severe pain and paralysis of the thighs developed associated with dark urine; incomplete recovery over 2 months	Spectroscopic	None	
Jasinski, Brutch [6]* 1952	43, M	2½ day coma due to ingestion of wine and sedatives followed by severe pain and swelling in both legs associated with dark urine; serum non-protein nitrogen rose to 252 mg./100 cc.; able to walk after 1 month	Spectroscopic	"Fish flesh appearance" with necrosis	
Elek, Anderson [38] 1953	41, F	3 days after a minor fall while drinking, marked tenderness and swelling of the calf muscle developed; dark urine occurred in 24 hours	Spectrophotometric	Evidence of previous muscle disease without vascular occlusions	Considered ischemic muscle damage by others
Hed [7] 1955 Case 5	53, M	An alcoholic had 4 episodes of aching and swelling in both calves; able to perform heavy work between attacks; last attack associated with dark urine, hyperkalemia and death in 24 hours	Spectroscopic	Extensive necrotic changes in muscles; lower nephron nephrosis; fatty liver	
Case 4	42, M	Onset at age 31 of yearly recurrences at Christmas of muscular pain associated with fever and dark brown urine; no relationship to exertion but always following an alcoholic bout; able to do heavy work between attacks	Spectroscopic	Minimal changes	Normal glucose tolerance tests; transient urea retention
Fahlgren [8] 1957 Case 1	48, M	Single episode of generalized muscle aching with swelling of the right shoulder and arm after a drinking bout; anuria for 9 days with death; alcoholic for many years	No	Autopsy-foci of necrosis with fragmentation; degenerative changes in renal tubules	Hyperkalemia with uremia
Case 2	45, M	Alcoholic, hospitalized for depression, developed severe aching, tenderness and swelling in lower trunk and extremity muscles after an overdose of barbiturates; dark urine for 24 hours	Spectroscopic	Swelling and hyalinization with loss of structure and vacuolization	

* Quoted in [7].

† Previously reported [49-51].

‡ These authors have seen two more cases since their recent report. In one, the patient died with acute renal failure despite hemodialysis [59].

§ Case to be reported. Included here through the courtesy of Department of Metabolism, Walter Reed Army Hospital.

¶ Quoted in [77].

** See Addendum.

TABLE II
LABORATORY DATA, CASE I

	Hospital Day				
	1	3	14	22	28
Urine output (ml./24 hr.)	400	2,565	4,435	...	3,300
Blood urea (mg./100 cc.)	28	72	65	27	24
Blood creatinine (mg./100 cc.)	1.7	3.7	2.7	...	2.0
Potassium (mEq./L.)	4.9	5.8	4.5	5.0	4.2
Serum total bilirubin (mg./100 cc.)	0.3	0.4	0.2
White blood cells (per cu. mm.)	32,000	56,000	21,000	9,000	12,000
Differential % segmented forms	86	84	82	...	68
Hematocrit (vol. %)	49	44	28	32	40
Reticulocyte count (%)	0.1 on 9th day		0.6	1.2	...
Bone marrow	Myeloid hyperplasia, erythroid hypoplasia on 10th day				

Approximately one year later on March 14, 1959, she was seen in the Emergency Room of the University of Virginia Hospital with a history of malaise, myalgia and a low grade fever for two days. Shortly after a thirty minute walk out of doors, muscular pain and spasm developed, becoming most prominent in the lower extremities, chest and abdomen. She was found to have a temperature of 101°F., the tonsils were slightly enlarged, and there was diffuse tenderness and muscular spasm in the upper part of the abdomen. Physical examination and roentgenograms of the chest were within normal limits. Examination of the urine revealed it to be of port wine color; it gave a 4-plus benzidine reaction, 4-plus albumin, and contained 3 to 4 red blood cells and numerous clumps of white blood cells per high power field. The diagnosis of an infection of the urinary tract was made and the patient was treated with acetyl sulfamethoxy-pyridazine. During the next eight hours muscular weakness progressed and breathing difficulty developed to the extent that cyanosis was noted by the family. The patient therefore returned to the hospital and was admitted to the Medical Service.

Past history obtained from the mother, in addition to that already described, revealed that the patient had had muscular aches and pains following moderate exertion since eight and a half years of age. To her knowledge there had never been associated dark urine. All previous episodes had been relatively mild, occurred approximately two to three hours after exertion and persisted for thirty-six to forty-eight hours.

Physical examination at this time revealed an alert white woman in acute respiratory distress with cyanosis. In addition to the findings recorded in the emergency room, there was respiratory difficulty and muscular weakness was noted in the trunk and lower extremities. The blood pressure was 140/90 mm. Hg, pulse 120 per minute and respirations 36 per minute.

The respirations were gasping, with utilization of accessory respiratory muscles. Chest cage movement was minimal and the diaphragm descended only 2 cm. with each inspiration. An expiratory vital capacity was recorded at 400 cc. On auscultation, wheezes and rales were absent, but air exchange was poor. The patient was unable to sit up without assistance, to stand or even to lift the extremities from the bed. The strength in the upper extremities was normal. Knee, ankle and abdominal reflexes were absent but the biceps and triceps reflexes were normal. No pathological reflexes were elicited and the sensory examination was completely normal. No evidence of muscular atrophy was present. Pelvic examination revealed parous introitus, normal menstrual bleeding, and no findings suggestive of pregnancy.

After admission the patient's respiratory exchange became inadequate, requiring the use of a mechanical respirator which quickly corrected the cyanosis. Because of her inability to void, she was catheterized and the urine was again port wine in color. The results of tests for albumin and benzidine reaction were 4 plus. Microscopic examination revealed only a few white cells and no red blood cells. Later studies (Figs. 1 and 2) demonstrated the presence of myoglobin in the urine and established the diagnosis of idiopathic paroxysmal myoglobinuria. The plasma was clear at this time and remained so.

After respiratory assistance was established, the patient stated that she had taken turpentine eight hours prior to her visit to the emergency room, as she had done without harmful effect one year before in an attempted abortion. This was supposedly ingested during the walk taken prior to the development of her acute symptoms. This information caused some diagnostic confusion until the nature of the abnormal urinary pigment was determined and further family and past history were obtained. Later the use of turpentine was repeatedly denied and this point remains uncertain.

On the third hospital day a tracheotomy was required because of the patient's inability to handle respiratory secretions. At this time hypotension also developed but responded well to the intravenous administration of vasopressor drugs. Therapy with the latter was discontinued gradually after four days but respiratory assistance was necessary for fourteen days. The tracheotomy tube was removed on the twenty-second day. Muscular tenderness was insignificant after the third day and, even though weakness persisted for twenty-five days, muscle atrophy was never noted. The patient was able to sit up in eighteen days and to walk about the ward by the twenty-second day. The color of the urine became normal in twenty-four hours although at this time microscopic hematuria developed. Oliguria was present for the first twenty-four hours, followed by an urinary output greater than 2,500 cc. per day.

Pertinent laboratory data are shown in Table II.

The course, although complicated by an infection of the urinary tract, was one of slow improvement after the fourth day. An anemia developed by the sixth day. This was characterized by normochromic microcytic indices, low reticulocyte count, normal serum bilirubin, low serum iron and increased latent iron-binding capacity. Several stool examinations for occult blood were negative. The hematocrit rose gradually over a two-week period with ferrous sulfate as the only therapy. With the exception of persistently low urinary specific gravity, the patient seemed to recover completely and was discharged on the thirtieth hospital day.

When seen in follow-up, six weeks after discharge, she was asymptomatic. The urinalysis revealed a pH of 5.5, specific gravity of 1.002, no albumin or sugar, 2 to 4 white cells, no red cells and an occasional granular cast. The blood urea nitrogen was 15 mg. per cent.

CASE II. A. T. (U. V. H. 278803), the fifteen year old sister of M. T. (Case I), was first admitted to the Pediatric Service at the University of Virginia Hospital because of an acute bronchitis when she was twenty-eight months old. She was considered to be otherwise normal at the time. At twelve years of age she was again admitted to the Pediatric Service with diffuse pain in the thighs and lower portion of the abdomen associated with anorexia and malaise. These symptoms had come on following strenuous exertion. The temperature was 99.4°F., blood pressure 130/80 mm. Hg, pulse 112 per minute, respirations 36 per minute. There was muscular soreness involving the neck, abdomen and calves, the patient being unable to sit down unassisted. The initial white blood cell count was 22,000 per cu. mm. with 83 per cent polymorphonuclear leukocytes, following which the count decreased to 13,500 per cu. mm. after five days. The initial urine specimen was dark brown in color and gave a 4-plus benzidine reaction. Studies for porphyria were negative. Only three to six red blood cells per high power field were noted. The serum was normal in color and the serum bilirubin normal. During the first week in the hospital, the urea rose to 114 mg. per cent, the creatinine to 3.5 mg. per cent with poor phenolsulfonphthalein excretion, but the serum potassium remained normal. After seven days the urine became normal in color, and evidence of renal impairment disappeared in fourteen days. In an unsatisfactory spectroscopic examination, the urinary pigment was thought to be hemoglobin. Cystoscopy and retrograde pyelography revealed no abnormalities. The patient was asymptomatic after four days and was discharged on the seventeenth hospital day.

On subsequent clinic visits she was asymptomatic and repeated urine examinations showed a specific gravity varying from 1.014 to 1.020, with repeatedly negative benzidine reaction. However, her mother stated that the patient had complained of pain in the

extremities and muscles following exertion during this period. Four and a half months after discharge an episode of three days' duration occurred, necessitating readmission to the Pediatric Service. This attack was unrelated to exertion and was characterized by severe muscle pain which inhibited movement of the extremities, trunk and, to a lesser degree, the neck. The initial temperature was 99°F. but rose to 102°F. on the following day and returned to normal in forty-eight hours. The blood pressure was 120/80 mm. Hg, respirations 26 per minute and pulse 122 per minute. The musculature of the extremities was tender, any movement produced pain. The spleen was palpable 2 cm. below the left costal margin. The white cell count was 14,700 per cu. mm. with a predominance of polymorphonuclear leukocytes. The urine was dark reddish brown in color and gave a 4-plus benzidine reaction; after the second hospital day it was normal. Again the serum was normal in color and the serum bilirubin was normal. Urinary studies for porphyrins, bilirubin and urobilinogen were non-contributory. The serum urea and potassium determinations were normal, but the phenolsulfonphthalein excretion was again decreased. The diagnosis of idiopathic paroxysmal myoglobinuria was suspected at this time but excretion of the abnormal urinary pigment had ceased before appropriate studies could be performed. After three days the patient was asymptomatic; she was discharged with instructions to avoid strenuous exertion.

On follow-up after two weeks the patient was asymptomatic, but the urine was benzidine-positive. She did not return again until October 23, 1958, one year later, when admission to the Medical Service was necessary. One week before admission she had a mild infection of the upper respiratory tract and, the day prior to hospitalization, a sore throat, stiff neck, occipital headache, fever and severe muscle aching which limited movement of the arms and thighs. The mother stated that the patient had complained of pain in the biceps and calf muscles after playing, but without associated dark urine. The temperature was 103°F., blood pressure 120/80 mm. Hg, pulse 140 per minute, respirations 28 per minute. Bilateral tonsillar enlargement with exudate was present. Muscle pain on motion was noted in the extremities, neck and lower portion of the back, but there was minimal tenderness to direct pressure. The liver and spleen were moderately enlarged and the patient was noted to be menstruating. A white blood cell count was 22,000 per cu. mm., again showing predominance of polymorphonuclear leukocytes, with return to 8,000 per cu. mm. in three days. The hematocrit was normal, as had been noted on all previous admissions. The initial urine specimen obtained on admission was dark brown in color and contained innumerable red blood cells thought to be due to menstruation. On subsequent urinalyses, however, the hematuria persisted but the color of the urine became normal after twenty-four

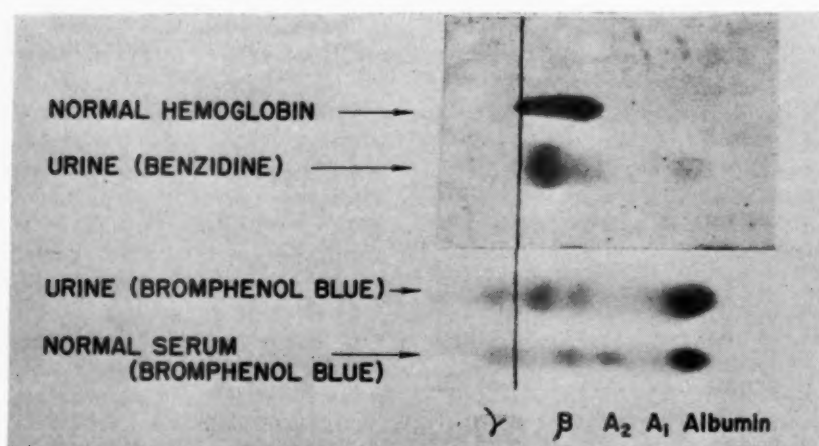


FIG. 1. Case 1. Paper electrophoresis of the urine, AA hemoglobin and normal serum. The top half of the strip is stained with benzidine, the lower half with bromphenol blue. The urine shows a serum protein pattern with the myoglobin spot between beta and gamma globulin. Methemalbumin is seen as the benzidine-positive spot in the albumin fraction of the urine.

hours. The initial urine specimen was inadvertently discarded, and urine obtained on the fifth hospital day contained no abnormal pigment.* Results of a blood urea and phenolsulfonphthalein excretion test were normal. The fever subsided and all symptoms completely disappeared after the second hospital day.

The patient has been seen on one occasion in January 1959, two and a half months after discharge, for another reason and was asymptomatic. In June 1959, the patient's mother reported that the muscular pain following exertion has continued.

These patients (Cases I and II) are two of six siblings, all female. (Table III.) No history of symptoms suggesting myoglobinuria or other disease is present in the family line including parents, grandparents and great-grandparents. The only familial disease noted is epilepsy, which is present in both families. There is no history of consanguinity.

METHODS OF STUDY

The urine which was tested was the initial urine specimen obtained by catheter from M. T. (Case I) on admission. The color was dark red, benzidine-positive and gave a strongly positive reaction for protein. The pH was 6. No red blood cells were present. The urine had remained in storage at 4°C. for twenty-one days before electrophoresis and forty-five days before spectrophotometric study.

Filter paper electrophoresis was performed according to the method of Smith and Conley [40] for hemoglobin electrophoresis. Veronal buffer at pH 8.6 and ionic strength 0.06 was used. Normal serum, AA hemoglobin and 0.05 ml. of the urine were subjected to a current of 350 volts for three hours. The part of the strip with the urine and the hemoglobin solution was stained with benzidine according to the

* During recent attack myoglobin was demonstrated electrophoretically by Dr. J. T. Carpenter.

method described by Lathem and Worley [42]. The rest of the strip was stained with bromphenol blue. Figure 1 shows the results of the electrophoresis. As can be seen, the urine contained a complete spectrum of serum proteins with an abnormal peak between the beta and gamma globulins. This portion was benzidine-positive, thus indicating it to be myoglobin. The mobility of this component is consistent with that reported for myoglobin by Singer et al. [44] who demonstrated that myoglobin migrated even slower than hemoglobin S at pH 8.6. We confirmed this finding on runs using the patient's urine and hemoglobin S. On further study it was found that the patient's hemoglobin and serum electrophoresis were normal. Lathem has shown that hemoglobin in the urine migrates identically with free hemoglobin in the plasma [43], thus being further toward the anode than myoglobin.

Figure 1 also demonstrates a faint but definite benzidine-positive spot in the urine albumin portion indicating the presence of methemalbumin.

TABLE III

Sib-ling	Age (yr.)	Sex	Status	Symptoms of Myoglobinuria
1	19	F	Alive; mentally defective; has seizures	No
2	...	F	Died of pneumonia at 4½ yr.	
3	17	F	Alive; has seizures	Yes; similar to cases I and II but without dark urine
4	16	F	Alive (Case I)	See text
5	15	F	Alive (Case II)	See text
6	11	F	Alive and well	No

The absorption spectrums of the urine at pH 6.0, diluted 1:5 with distilled water, with and without the addition of potassium ferrocyanide, were determined in a Cary recording spectrophotometer. Figure 2 shows the almost identical absorption curves of the diluted untreated and ferricyanide-treated urine, indicating that the pigment present was metmyoglobin. The curves are identical with those previously described for acid metmyoglobin with maximums at 630 and 500 $m\mu$ [44,46].

COMMENTS

The clinical picture of idiopathic paroxysmal myoglobinuria has been well described previously [4,7,25,29,37]. The attacks frequently begin following exertion of varying types and severity, but at times hard labor or vigorous exercise may fail to produce symptoms. In some patients an episode may be predictably produced by a known amount of exertion while in others there is marked variation in the physical activity preceding the attack. Occasionally, attacks are precipitated by infection and fever, as in our cases [12,27,32].

Muscle pain of varying severity, most often affecting the calves, thighs and back, is noted first, often associated with stiffness and tenderness. Systemic symptoms may ensue, including chills, fever, anorexia and malaise. The course varies markedly, ranging from progressive to almost complete paralysis with respiratory embarrassment as in our Case I, to rapid subsidence with minimal or no weakness as in our Case II. Pain and tenderness usually disappear in a day or two but may last up to a week. The urine, which may become dark brown, is usually somewhat red at first. It becomes discolored in a few hours after the onset of pain and usually clears in about twenty-four hours, although the abnormal color may persist up to seven days. Renal involvement is variable and may not be evident. Transient oliguria and azotemia may be seen, as in our Case II, or the manifestations of acute tubular necrosis may appear, as in our Case I. Red blood cells are not usually seen in the first urine excreted but may appear in large numbers thereafter, as in our Case I. Proteinuria is usually present.

Evidence for hemolysis is absent and anemia does not occur unless renal failure ensues. Extreme leukocytosis, predominantly polymorphonuclear, is common, as seen in our two cases.

The diagnosis can be made on clinical grounds alone if the picture is typical. Paroxysmal hemoglobinuria, porphyria and hematuria are, for

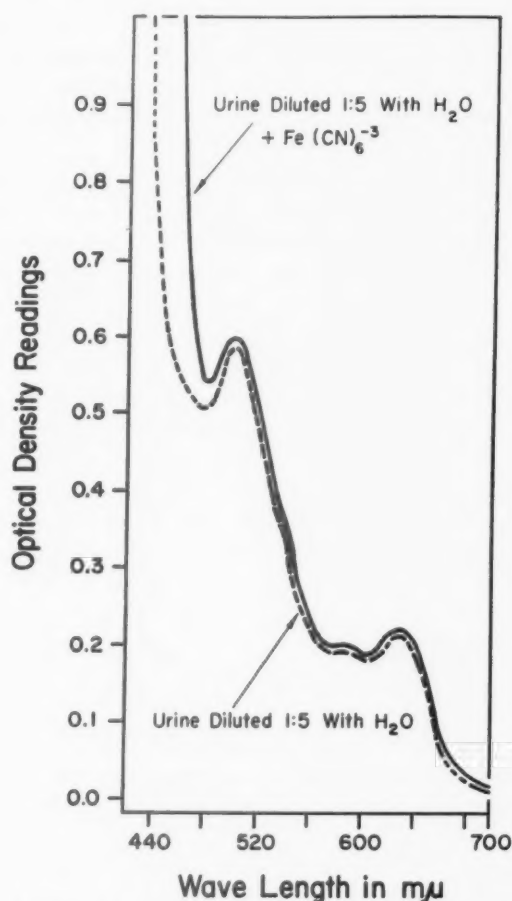


FIG. 2. Case I. Spectrophotometric analysis of the urine. The characteristic spectrum of acid metmyoglobin is seen, with maximums at 630 and 500 $m\mu$.

practical purposes, ruled out if clear serum is found along with discolored, benzidine-positive urine free of red blood cells. For proof, however, the urine pigment must be demonstrated to be myoglobin. This is best accomplished by spectrophotometry or electrophoresis. A simple test to differentiate myoglobin from hemoglobin in the urine has been described by Blondheim et al. [59]. Spaet et al. [25] have listed a differential diagnosis of paroxysmal pigmenturia.

The explanation for the clear plasma and dark urine with myoglobinuria, as contrasted to the always discolored plasma associated with hemoglobinuria, is based on the observation that myoglobin is excreted by the kidneys at a much lower plasma level and is cleared twenty-five times faster than hemoglobin [47]. The plasma level at which hemoglobin appears in the urine is about 100 to 150 mg. per 100 ml. [43,47,52] which is two to four times the concentration needed to color the plasma [4]. The level for

myoglobin is 15 to 20 mg. per 100 ml. of plasma [4,43,47] which is approximately half the concentration necessary to produce discoloration. A pink color to the urine visible upon inspection, has been noted at a myoglobin concentration of about 25 mg. per 100 ml. [37].

This difference has previously been ascribed to differential glomerular permeability related to the fact that the myoglobin molecule is one-fourth the size of the hemoglobin molecule. However, the studies of Laurell and Nyman [53] and then of Lathem [42,43] demonstrated that hemoglobin did not appear in the urine until the plasma hemoglobin-binding capacity (haptoglobin) was exceeded. It seemed, therefore, that perhaps myoglobin was not bound by plasma proteins, or if so, in low concentration and thus had a lower "renal threshold." Recent work of Javid et al. [48,60] has demonstrated that myoglobin is not bound by haptoglobin. These investigators, utilizing starch gel electrophoresis, found no evidence for binding of myoglobin by human serum. Lathem, however, has reported protein binding of myoglobin by dog plasma [55]. It is worthy of note that although on electrophoresis of the urine in Case 1 there was a complete serum protein pattern, no benzidine-positive material was seen in the alpha-2 site where haptoglobin is found [42], or in the beta site of the heme-binding beta globulin [56,57]. Methemalbumin was present, as indicated by the benzidine-positive spot in the albumin fraction.

The underlying defect predisposing to spontaneous muscle breakdown is as yet unknown. It seems most likely to be an abnormality in muscle metabolism. Some cases strongly suggest genetic transmission. No consistent metabolic changes have been reported, although several patients have had an abnormality of carbohydrate metabolism [7,37] and two were found to have an increase in ketosteroid excretion [4,15]. Electrophoresis of the myoglobin from one patient showed a mobility identical with that of normal myoglobin [45], as in Case 1.

No definite mode of inheritance has been established, although Bowden et al. [4] favor the possibility that a recessive gene is involved. The two cases reported herein are in keeping with this possibility, although environmental factors cannot be ruled out.

Histological studies of muscle from the patients with this syndrome have varied with the stage of the disease [28,29]. Degenerative and

necrotic changes have been described most often, although during [25] or shortly after [7,60] an attack the changes may be minimal or absent. Biopsy specimens taken between attacks revealed no abnormalities in two cases [37,32].

Management of the acute episode depends on the severity. No specific treatment can be offered since the etiology is unknown. Pain relief, bedrest, adequate hydration and close observation are the main points. Artificial support of respiration may become necessary. Careful fluid balance must be maintained and if renal shutdown becomes evident this should be treated accordingly. Long-term management of the patient with frequent recurrences should stress, of course, avoidance of excessive exertion or other inciting factors believed to precipitate symptoms. However, attacks are at times associated with routine activity.

The chances of recovery from an attack are relatively good but eight deaths directly related to this syndrome have been reported in the fifty-one cases reviewed herein. Death resulted from acute renal failure in four cases [8,22,36,59], muscle soreness followed by sudden unexplained death in two cases [4], complete paralysis with respiratory failure [23] and hyperkalemia [7].

Although only a few of the reported cases have been followed for a sufficiently long time it appears that atrophy of muscle is unusual in this condition unless it is associated with a classifiable type of muscle disease.

SUMMARY

Two cases of idiopathic paroxysmal myoglobinuria occurring in sisters are reported, and the literature on myoglobinuria is reviewed. A brief description of the syndrome is presented including a discussion of the electrophoretic properties and renal excretion of myoglobin.

Acknowledgment: We would like to thank Dr. Donald Kupke for performing the spectrophotometry; Dr. C. Hoch-Ligeti for assistance with the electrophoresis; Dr. William Parson and Dr. Oscar Thorup for reviewing the manuscript.

ADDENDUM

Since this paper was submitted, several reports containing six additional cases have been published [62-65]. The patient described by Kreutzer et al. [14] has been further studied by Schmid and Mahler [66]. They demonstrated a defect in the phosphorylase system of the muscle which eliminates anaerobic glycogenolysis as a source of energy for muscular contraction.

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The Renal Concentrating Defect in Sick Cell Disease*

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IN Herrick's first description of sick cell anemia in 1910 [1] he observed that the urine flow was slightly increased in amount and of low specific gravity, varying in concentration between 1.010 and 1.014. The urine output averaged 2,000 ml. per day, was acid in reaction, and contained a trace of albumin and a few granular and hyaline casts. In subsequent early reports the persistently low urinary specific gravity again was mentioned [2-5]. Since then many reports in the literature allude to the fact that patients with sickle cell disease cannot elaborate a concentrated urine. In one study of nineteen patients with sickle cell disease the maximum specific gravity of the urine after an eighteen-hour fast varied between 1.007 and 1.018 [6]. In another series of cases of sickle cell disease the maximum urinary osmolality averaged 420.7 ± 72 mOsm./kg. H_2O [7]. Henderson [8] reported a series of fifty-four cases of sickle cell disease in which only two patients were able to concentrate the urine beyond a specific gravity of 1.015. Kunz et al. [9,10] found that thirteen of fourteen children with sickle cell anemia could not elaborate a urine of greater concentration than 1.015 despite a fifteen-hour period of water deprivation and the subcutaneous administration of Pitressin.® It is clear that inability to concentrate the urine is a consistent manifestation of sickle cell disease.

Impaired concentration of the urine also occurs in sickle cell trait, but less consistently. Thus in one report 69 per cent of a group of patients with sickle cell trait showed impaired ability to concentrate the urine [11]. In another series the maximum osmolality of the urine in

patients with sickle cell trait averaged 604 ± 154 mOsm./kg. H_2O [7].

Since patients with the trait are not generally anemic, the impaired ability to concentrate the urine cannot be attributed to anemia *per se*. Persons with the sickle cell trait who had hemoglobin concentrations of 14.2 and 13 gm. per cent, respectively, showed impaired capacity to concentrate the urine [6]. Thalassemia and other hemolytic, non-sickle cell anemias are not associated with any defect in the ability to concentrate the urine [6]. Severe anemia of long duration, of whatever cause, does not impair the capacity of the kidney to elaborate a concentrated urine.

It has been shown that, at least early in the course of sickle cell anemia, the inability to concentrate the urine is reversible [11]. After receiving a transfusion of normal blood, young, hyposthenuric "sickle cell" patients§ were able to concentrate the urine for several months. This reversibility of the defect was noted only in patients under the age of five years. In adults, the concentration defect did not improve with transfusions of normal blood.

Patients with sickle cell anemia appear to have an intact osmoreceptor-hypothalamic-posterior pituitary system [9]. Hyperosmolar infusions in children with sickle cell anemia evoked a moderate antidiuresis. The decrease in urine flow, while not as pronounced as that in the normal subject, denotes some sensitivity of the posterior pituitary to appropriate stimulus, and the capacity of the kidney to respond to endogenous hormone.

§ Refers to patients with either sickle cell disease or sickle cell trait.

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TABLE I
CLINICAL DATA ON SICKLE CELL SUBJECTS

Patient	Diagnosis	Clinical Data	Hemo- globin Concen- tration (gm. %)	Hemo- globin Electro- phoresis	Blood Urea Nitrogen (mg. %)	Urinaly- sis	Maxi- mum Urine (specific gravity)	Glomerular Filtration Rate (cc./min.)
J. C.	Sickle cell disease	19 year old Negro woman studied after recovery from pneumonia	7.0	All S	6	Normal	1.013	155
N. L.	Sickle cell disease	53 year old Negro woman admitted for studies during quiescent phase of disease	6.0	All S	21	Normal	1.012	60
L. B.	Sickle cell disease	20 year old Negro man admitted for therapy of leg ulcers	6.5	94% S	9	Normal	1.012	130
D. G.	Sickle cell disease	26 year old Negro man studied after recovery from sickle cell crisis	8.5	75% S	8	Normal	1.012	135
M. C.	Sickle cell trait	26 year old Negro woman studied after recovery from pelvic inflammatory disease	10.5	A and S	8	Normal	1.014	88
M. M.	Sickle cell trait	48 year old Negro woman studied in the course of work-up for mild essential hypertension	12.9	A and S	13	Normal	1.014	87
C. M.	Sickle cell disease	6 year old Negro boy studied after recovery from sickle cell crisis	8.3	All S	12	Normal	1.014	30
I. C.	Sickle cell trait	25 year old Puerto Rican woman studied after spontaneous abortion	11.5	A and S	9	Normal	1.014	115

The changes in other modalities of renal function, such as glomerular filtration rate and renal blood flow, in patients with sickle cell disease are not so consistent. The glomerular filtration rate as determined by the sodium thiosulfate method was found to be diminished in patients with sickle cell anemia, but normal in those with sickle cell trait [12]. Protracted anemia not due to sickle cell disease is itself often associated with reduced effective renal plasma flow, glomerular filtration rate and Tm diodrast [13]. On the other hand, in Mediterranean anemia the total renal plasma flow and glomerular filtration rate were found to be greatly elevated in five of seven patients [14]. In subjects with sickle cell disease, the glomerular filtration rate, effective renal plasma flow and TmPAH were reported to be supernormal during early adulthood [15]. Between the ages of twenty and thirty these functions began to decline [16], the most conspicuous changes being noted in the glomerular filtration rate. After the third decade all the functions

were somewhat depressed. It is difficult to draw final conclusions from these conflicting data but it seems reasonable to assume that throughout the early and intermediate phases of the course of sickle cell disease the glomerular filtration rate, TmPAH, effective renal plasma flow and effective renal blood flow are normal at a time when the concentrating defect is consistently in evidence.

The majority of patients with sickle cell type hemoglobin are found to have some arterial oxygen desaturation. A shift to the right of the oxyhemoglobin dissociation curve in such subjects has been implicated as the factor primarily responsible [17]. Furthermore, the pulmonary dysfunction frequently noted in sickle cell patients and attributed to infarction of pulmonary parenchyma and/or shunting of blood through non-aerated lung will exaggerate the degree of oxygen unsaturation [17,18]. The administration of 100 per cent oxygen for two hours to patients with sickle cell anemia did not increase the

TABLE II
RESPONSE TO HYDRATION AND PITRESSIN ADMINISTRATION IN SICKLE CELL SUBJECTS

Patient	H ₂ O Load			Pitressin (1,800 mUnit/hr.)		
	Time (min.)	Urine Flow (ml./min.)	Osmolality U (mOsm./kg. H ₂ O)	Time (min.)	Urine Flow (ml./min.)	Osmolality U (mOsm./kg. H ₂ O)
M. M.	30	1.01	331	30	9.00	160
	30	4.05	121	30	5.01	326
	30	8.90	80	30	5.56	330
	30	12.33	46	30	5.20	345
M. C.	35	0.40	387	30	5.66	72
	30	1.36	287	30	1.27	304
	30	3.60	...	30	1.00	303
	30	10.50	48	30	0.90	330
J. C.	30	14.67	28	30	8.83	44
	30	18.00	23	70	1.14	348
				25	1.08	370
				27	1.11	367

capacity to elaborate a concentrated urine [77].

In the present study a series of experiments were performed in isosthenuric sickle cell subjects in whom observations were made on the response to water loads and subsequent administration of Pitressin as well as to alterations in filtered solute loads under conditions of maximum hydropenia. An attempt will be made to interpret these findings in the light of the current theory concerning the renal mechanisms for elaboration of a concentrated urine.

EXPERIMENTAL METHODS AND RESULTS

Three types of experimental procedures were performed in eight subjects, of whom five had sickle cell disease and three had sickle cell trait. Six of the eight subjects were under the age of thirty. All of the patients were afebrile and in excellent condition at the time of study, without any evidence of cardiac, pulmonary or hepatic failure. The patients with sickle cell disease had anemia of modest degree, those with the trait had normal hemoglobin concentrations at the time of the experimental procedure. Except for the persistent isosthenuria which was present in each patient, no other manifestation of renal involvement was evident. (Table I.)

In the first experimental protocol, three subjects (one with sickle cell disease and two with sickle cell trait) were hydrated with an oral water load of 2,000 cc. After a sustained peak of urine flow was achieved, the oral intake of water was maintained at the level of

urine output and Pitressin was infused at a rate of 30 mU./kg./hour. The changes in the rate of urine flow and urine osmolality were measured. (Table II, Fig. 1.) During the period of peak diuresis, urine flows reached 12.3, 10.5 and 18 cc./minute, the urine osmolalities falling to 46, 48 and 23 mOsm./kg. H₂O, respectively. When Pitressin was administered, the urine flows decreased to 5.20, 0.9 and 1.1 cc./minute, and the urine osmolalities rose to 345, 330 and 370 mOsm./kg. H₂O, respectively. These final urine concentrations compared favorably with levels observed under conditions of maximum hydropenia.

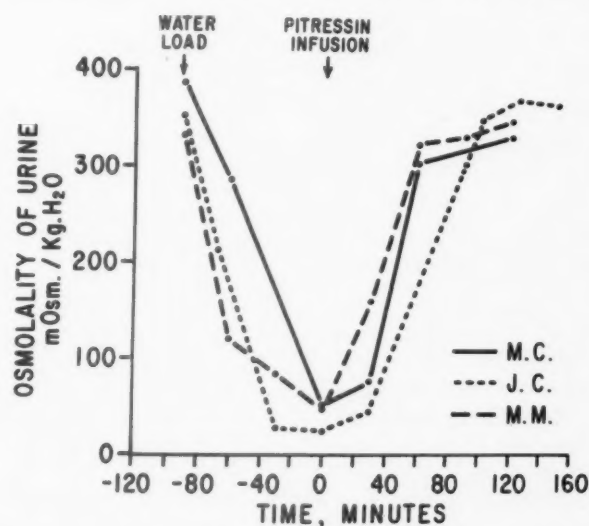


FIG. 1. Response of the sickle cell subject to a water load and the subsequent administration of Pitressin.

TABLE III
EFFECTS OF REDUCTION IN FILTRATION RATE

Patient	Time (min.)	Urine Flow (ml./ min.)	Inulin Clear- ance UV/P (ml./ min.)	Urine									
				Osmolality		Sodium		Chloride		Potassium		Urea	
				U (mOsm./ kg. H ₂ O)	UV (μOsm./ min.)	U (mEq./L.)	UV (μEq./min.)	U (mEq./L.)	UV (μEq./min.)	U (mEq./L.)	UV (μEq./min.)	U (mM/L.)	UV (μM/min.)
Sickle Cell Subjects with Hydropenia													
M. M.	(36)	(2.89)	(87)	(521)	(1,510)	(151)	(438)	(143)	(416)	(40)	(105)	(76)	(205)
	24	2.63	86	535	1,407	148	388	139	364	49	127	74	205
	20	0.65	76	509	331	71	46	88	57	134	87	132	86
	57	0.12	29	524	63	51	6	75	9	149	18	130	16
	25	0.34	97	502	171	13	4	28	10	131	45	169	57
	16	0.84	101	494	415	17	14	38	32	141	118	191	160
M. C.	(47)	(1.27)	(88)	(413)	(525)	(106)	(136)	(131)	(167)	(57)	(72)	(93)	(118)
	26	1.00	65	413	413	98	98	130	130	58	58	94	94
	22	0.41	54	448	187	51	21	106	43	89	37	119	49
	66	0.23	31	338	78	38	9	95	22	94	22	63	14
	10	1.65	101	323	533	56	92	107	177	83	136	65	107
J. C.	(58)	(1.33)	(155)	(418)	(556)	(115)	(153)	(103)	(138)	(78)	(103)	(48)	(63)
	38	1.18	118	421	496	108	128	100	118	82	97	44	52
	42	0.19	38	414	79	70	13	80	15	104	20	42	8
	27	0.37	147	380	141	14	5	46	17	122	45	66	24
	17	0.59	120	398	235	20	12	60	35	140	83	79	47
D. G.	(49)	(0.93)	(135)	(374)	(350)	(15)	(14)	(35)	(33)	(78)	(72)	(170)	(158)
	38	0.22	92	351	77	14	3	30	7	82	18	151	33
	58	0.47	70	325	153	5	3	10	5	60	28	141	66
	25	0.26	48	334	87	5	1	8	2	64	17	165	43
	26	1.19	136	338	403	6	7	11	13	73	86	163	194
Normal Subjects with Hydropenia													
H. L.	(64)	(0.35)	(131)	(985)	(345)	(131)	(46)	(151)	(53)	(157)	(55)	(141)	(50)
	50	0.24	86	953	229	108	26	121	29	182	44	137	33
	29	0.17	68	883	150	76	13	73	12	184	31	118	20
	39	0.24	89	923	222	107	26	106	26	177	43	140	34
L. J.	(90)	(0.65)	(90)	(820)	(583)	(100)	(65)	(134)	(87)	(186)	(121)	(60)	(39)
	28	0.29	50	852	241	103	29	112	32	204	58	48	14
	52	0.13	54	702	91	43	6	56	7	188	24	44	6
	45	0.20	70	830	176	41	8	57	11	228	46	55	11
I. M.	(98)	(0.27)	(68)	(1,027)	(277)	(141)	(38)	(133)	(36)	(105)	(28)	(245)	(66)
	40	0.22	55	1,029	226	150	33	143	31	97	21	271	60
	45	0.13	43	972	126	110	15	105	14	117	16	186	24
	52	0.21	52	951	200	113	24	74	15	120	25	205	43
C. R.	(58)	(0.85)	(133)	(920)	(782)	(134)	(114)	(144)	(122)	(115)	(98)	(125)	(106)
	29	0.78	103	727	567	140	109	128	100	118	92	127	99
	59	0.27	69	776	210	124	33	49	13	144	39	121	33
	36	0.12	70	774	93	63	8	17	2	181	22	105	13

Data in parentheses represent average of three control periods.

The rise in urine osmolality appeared within thirty minutes after the administration of Pitressin and was almost maximal within one hour. (Table II, Fig. 1.)

In the second group of studies the glomerular filtration rate was reduced in four sickle cell subjects in whom hydropenia had been induced by the administration of Pitressin (two with sickle cell disease and two with sickle cell trait), and the effect on the excretion of solute and water was measured. The four patients were fasted for eighteen hours and given 5

units of Pitressin tannate in oil the night before the experiment. On the following morning an infusion of inulin and Pitressin (200 mU./hour) was administered. This was continued until a steady state had been established. The blood pressure was then decreased by the intravenous administration of SC 1950 (1-ethyl-2, 6-dimethyllyptidine ethobromide), a ganglionic blocking agent, and/or the application of venous tourniquets to the thighs. During the control period and the period of hypotension, glomerular

filtration rate, urine flow, urine osmolality, and the rates of excretion of sodium, chloride, potassium and urea were measured. (Table III, Fig. 2A.) These results were then compared with the results of similar experiments performed in four normal hydropenic subjects. (Table III, Fig. 2B.) The methods used in these studies are presented elsewhere [19].

In the sickle cell subjects the control glomerular filtration rates were 87, 88, 155 and 135 ml./minute, averaging 116 ml./minute. (Table III.) The control glomerular filtration rates in the subjects with hydropenia only were 131, 90, 68 and 133 ml./minute, averaging 106 ml./minute. (Table III.) In the four subjects with sickle cell anemia, during the period of hypotension, the maximum fall in glomerular filtration rate was 67, 65, 75 and 77 per cent, with an average of 71 per cent. In the normal subjects the maximum fall in glomerular filtration rate recorded was 48, 44, 37 and 48 per cent, with an average of 44 per cent.

The control rate of urine flow in the sickle cell patients averaged 1.60 ml./minute whereas the control rate of flow in the normal subjects averaged 0.53 ml./minute. During the period of diminished glomerular filtration the rate of urine flow decreased similarly in both normal and sickle cell subjects, averaging 0.20 ml./minute in the sickle cell subjects and 0.14 ml./minute in the normal subjects. (Table III.)

Coincident with the marked fall in urine flow and filtration rate, the sickle cell subjects showed a consistent fall in urine osmolality, which was recorded as 30, 125, 41 and 49 mOsm./kg. H₂O, respectively (Table III), and averaged 14 per cent. In the normal subjects a similar percentile fall in total urine osmolality occurred under the same experimental conditions (Table III), averaging 13 per cent; however, the absolute falls were somewhat greater in view of the much higher control levels of urine concentration.

In both groups of subjects responding with a fall in filtration rate and urine flow there was a considerable decrease in the concentration of sodium in the urine, averaging 83 per cent in the normal subjects and more than 90 per cent in the sickle cell subjects. In both groups the urinary concentration of potassium increased somewhat, but because of the marked fall in urine flow there was a decrease in the rate of potassium excretion, averaging about 70 per cent in both normal and sickle cell subjects. The urinary concentration of urea remained unchanged or decreased slightly in both the normal and sickle cell subjects, so that the rate of urea excretion decreased about 75 per cent in both experimental groups. (Table III.)

Finally, four hyposthenuric sickle cell subjects (three with sickle cell disease and one with the trait) were exposed to the reverse experimental conditions. As in previous experiments, hydropenia was induced by an eighteen-hour fast and the administration of 5 units of Pitressin tannate on the night before the experiment. The following morning an infusion of

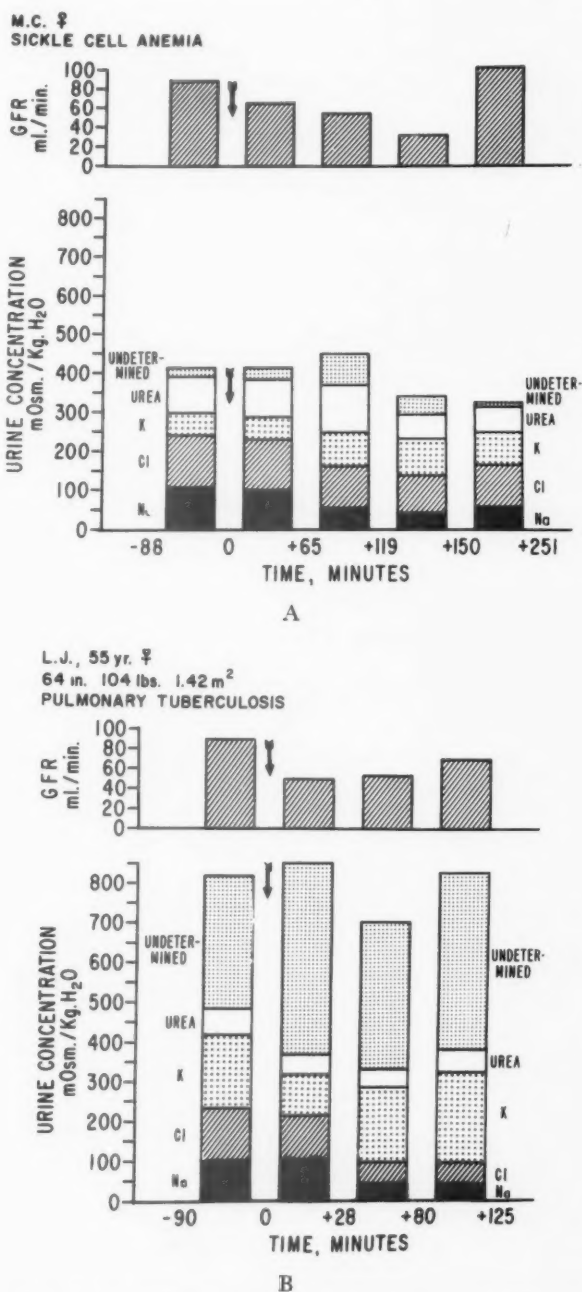


FIG. 2. A, the effect of a reduction in glomerular filtration rate on solute and water excretion in a hydropenic sickle cell subject. Arrows represent time at which blood pressure was reduced. B, the effect of a reduction in glomerular filtration rate on solute and water excretion in a hydropenic normal subject.

inulin and Pitressin (200 mU./hour) was started at the rate of 0.6 cc./minute until a steady state was achieved. Thereafter a separate infusion of hypertonic mannitol solution (25 per cent) was administered at an initial rate of 0.5 cc./minute and then at a gradually increasing rate until a maximum rate of urine flow approaching 20 to 25 per cent of the filtration rate was

TABLE IV*
EFFECTS OF MANNITOL LOADS ON URINE CONCENTRATION IN SICKLE CELL SUBJECTS

Patient Data	Time (min.)	Serum Osmolality (mOsm./kg. H ₂ O)	Urine Flow (ml./min.)	Urine Osmolality (mOsm./kg. H ₂ O)	Solute Excretion (Osm./min.)	TcH ₂ O (ml./min.)	% Total Filtered Load Excreted	% Filtered Chloride Excreted
N. L., a 53 year old woman with sickle cell disease, glomerular filtration rate: 60 ml./min., maximum TcH ₂ O 3.24 ml./min./100 cc. glomerular filtration rate	(76)	(277)	(2.20)	(377)	(829)	(0.72)	(5)	(3)
	14		2.14	377	807	0.70	5	
	16		2.14	373	798	0.67	5	3
	16	275	2.00	373	746	0.63	5	
	11		3.73	365	1,361	1.06	8	
	10		6.40	348	2,227	1.44	13	7
	13	288	8.92	332	2,961	1.51	17	
	10		11.00	334	3,674	1.94	23	
	9	305	12.11	330	3,996	1.94	22	14
L. B., a 20 year old man with sickle cell disease, glomerular filtration rate: 130 ml./min., maximum TcH ₂ O 3.17 ml./min./100 cc. glomerular filtration rate	(50)	(273)	(1.23)	(385)	(474)	(0.51)	(1)	
	26	272	1.08	383	414	0.44	1	1
	18		2.11	399	842	0.97	2	
	16		2.67	395	1,055	1.20	3	1
	19		3.24	391	1,267	1.40	4	
	19		5.67	390	2,211	2.43	6	
	10		7.60	378	2,873	2.92	8	4
	10		11.00	375	4,125	4.12	12	
	12		10.33	380	3,925	4.04	11	
	10		9.80	380	3,724	3.85	10	8
C. M., a 6 year old boy with sickle cell disease, glomerular filtration rate: 30 ml./min., maximum TcH ₂ O 7.59 ml./min./100 cc. glomerular filtration rate	(80)	(283)	(0.35)	(467)	(163)	(0.19)	(2)	(0.5)
	15		0.40	453	181	0.20	2	
	12		0.58	453	263	0.30	3	0.6
	10		0.80	460	368	0.43	4	
	10		1.30	453	589	0.67	7	
	15		2.47	449	1,109	1.23	12	2.0
	11		3.09	446	1,378	1.49	15	
	10		4.20	433	1,819	1.87	20	
	8	314	5.50	424	2,332	2.28	26	5.0
I. C., a 25 year old man with sickle cell trait, glomerular filtration rate: 115 ml./min., maximum TcH ₂ O 2.84 ml./min./100 cc. glomerular filtration rate	(86)	(273)	(0.75)	(487)	(365)	(0.59)	(1)	
	14	289	3.39	472	1,600	2.15	5	
	8		6.32	422	2,667	2.91	8	
	7		9.64	381	3,673	3.07	11	
	6		15.50	350	5,425	3.27	16	
	6		26.33	321	8,452	1.56	25	
	5	303	32.00	307	9,824	0.42	27	

* Data in parentheses represent average value of at least three separate control periods. After these data were obtained, the intravenous administration of 25% mannitol was begun.

achieved. Urine flow, urine osmolality, chloride concentration and filtration rates were measured throughout the control and experimental periods. Three subjects had normal glomerular filtration rates initially but a patient with sickle cell disease (N. L.), who had survived to the age of fifty-three, had a moderate diminution in filtration rate. (Table iv.)

As the rate of urine flow increased there was a slight progressive decrease in urine osmolality. (Table iv, Fig. 3.) Despite rates of solute excretion that averaged 20 per cent of the filtered load, the fall in urine osmolality averaged about 14 per cent, the

urine remaining distinctly hypertonic to plasma. In three subjects (N. L., C. M. and I. C.) in fact, the urine remained hypertonic to serum despite a rate of solute excretion reaching 23, 26 and 27 per cent of the filtered load. In Figure 3 the urine osmolalities in the sickle cell patients are compared to those recorded in normal subjects exposed to a comparable solute diuresis. In the same figure, the changes in the normal subjects and those in the sicklers are contrasted with those observed in comparable experiments by de Wardener and Del Greco in subjects with diabetes insipidus [38]. In the latter experiments the urine

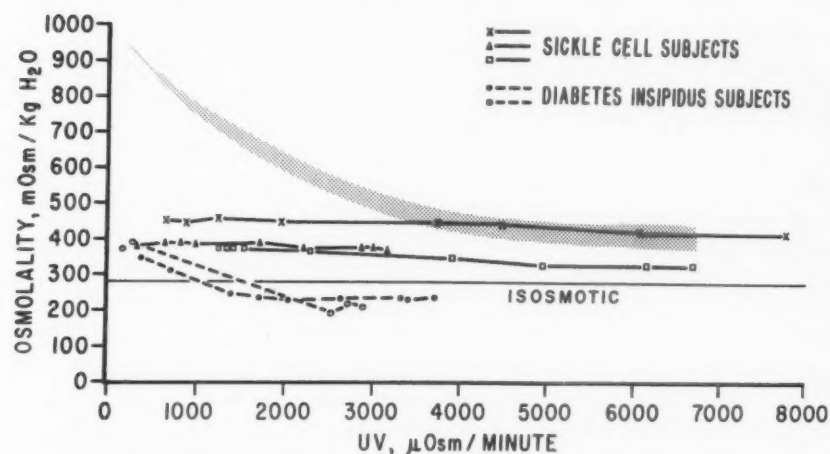


FIG. 3. Solute concentration of the urine following a mannitol load in normal (stippled area), sickle cell and diabetes insipidus subjects (the last from de Wardener and Del Greco [38]).

osmolality was brought to a level commensurate with that produced in the maximally hydropenic sickle cell patient by the administration of a small quantity of Pitressin. Thereafter an infusion of hypertonic mannitol solution rapidly produced a urine hypotonic to plasma.

Because of the meager fall in urine osmolality noted in the face of increasing solute loads in the patients with sicklemia, calculations of TcH_2O tended to show a progressive rise as urine flow increased towards 10 to 12 cc./minute. (Table iv, Fig. 4.) In Figure 4 solute clearances are plotted against urine flow so that the TcH_2O may be expressed as the horizontal distance between the slope of the curve reflecting the observed responses and the isosmotic line. At modest solute loads the TcH_2O in the sickle cell subjects increased to maximum values of 3.2, 3.2, 7.6 and 2.8 cc./100 cc. glomerular filtration rate. (Table iv.)

In Table iv the rate of chloride excretion, expressed as per cent of the filtered chloride load, is recorded as the solute load increases in the subjects with sickle cell disease. The progressive increase in this ratio is commensurate with that noted in normal subjects exposed to a comparable solute load.

COMMENTS

Considerable insight has been acquired recently into the mechanisms by which variations in urine osmolality are achieved [20,27]. It is generally accepted, on the basis of both direct and indirect evidence, that the first phase of solute and water absorption is effected isosmotically, the prime event presumably being the active transport of sodium; absorption of chloride and bicarbonate occurs by passive processes dependent upon electrochemical gradients established by the active process [22-24]. Thereafter water

diffuses across a freely permeable membrane, maintaining the concentration of the plasma ultrafiltrate. Isosmolality within the proximal tubule obtains regardless of the rate of solute flow [25].

A progressive rise in solute concentration from the outer layers of the medulla to the tip of the pyramid has been recorded within the descending loop of Henle and collecting tubule, and in the vasa rectae, all coursing in parallel through the medulla [20,27]. Achievement of this hypertonicity has been attributed principally to a counter current multiplier, the seat of which resides in the ascending loop of Henle where

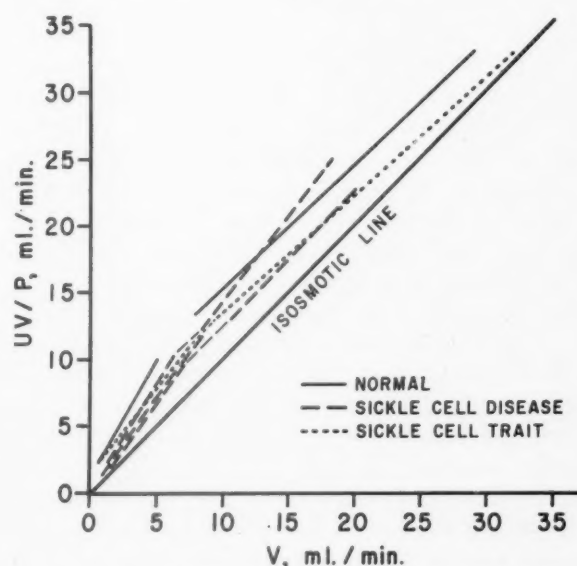


FIG. 4. Relation between solute clearance (UV/P) and urine flow (V) in normal and sickle cell subjects exposed to mannitol loads.

sodium is actively pumped out of the lumen [27]. The fluid within the descending loop is thought to be concentrated by the diffusion of water outward and/or by the inward diffusion of salt. The longer the loop and the slower the rate of flow, the more effectively is the solute concentrated towards the tip of the papilla [27,28]. The peculiar architecture of the vasa rectae permits these vessels to act as a counter current diffuser, maintaining a solute concentration within the vessels identical with that noted at the same level in the interstitium or in the descending loop of Henle. The proximity of the capillary loops enables solute to diffuse from the more hypertonic efferent branch to the afferent branch, thus tending to trap solute within the medulla. The diffusion of water occurs in the reverse direction, producing the same end result. As in the case of the counter current multiplier, the effectiveness of the diffuser is related in some inverse manner to the rate of blood flow [27].

As the tubular fluid ascends the loop, the continued outward extraction of sodium, in an area less permeable to water, results in progressive dilution of this fluid [25]. Urea, whether actively extruded at this site [29] or (more likely) diffused into the medulla from the adjacent collecting duct [19,30], likewise is confined by the circulation described.

In the proximal segments of the distal tubule, the continued outward transport of salt across a membrane relatively impermeable to water further enhances the degree of dilution. At this site antidiuretic hormone (ADH) allegedly plays its primary role, namely, the specific enhancement of tubular permeability to water [31,32]. In the presence of maximum quantities of this hormone, water diffuses out of the distal tubule until a maximum concentration of isosmolality is achieved at a site proximal to the collecting duct. The precise action of this hormone is determined by the quantity of solute absorbed at this site and the amount of water thereby set free, the rate of flow down the distal tubule, and the relative quantity of ADH available. Micropuncture data in the rat and hamster have suggested that, at least in these species, over a wide range of solute flow, maximum hydropenia permits the back diffusion of sufficient quantities of water to achieve isosmolality at the end of the distal tubule [25]. However, in man under conditions of maximum hydropenia, at high levels of solute excretion (30 to 50 per cent of that filtered), the occasional production of

urine hypotonic to plasma indicates that isosmolality at this site is not always achieved [33].

Thereafter the fluid enters the collecting tubules, which pass through the area of medullary hypertonicity. Here, too, ADH enhances the permeability to water so that the tonicity of the tubular fluid may approximate that of the adjacent medullary interstitium [37]. Again, the rate of flow at this site and the variable dilution of the fluid are important factors in determining whether or not osmotic equilibrium between the fluid within the collecting duct and that in the hypertonic medulla is achieved. Under conditions of diuresis, the medullary hypertonicity may be limited by the increased volumes of water which must be transported per unit time as well as by an increase in the rate of blood flow in the medulla, tending to decrease the effectiveness of the capillary solute trap [34]. Indirect data suggest that after water diffuses back, urea follows [19,30].

It has been suggested that ADH may play an additional role by enhancing outward transport of sodium in the ascending loop of Henle or by rendering the descending loop more permeable to water [35]. However, the evidence for such effects of ADH remains incomplete.

Returning to the renal defect in sicklemia, the inability to elaborate a urine of appropriate hypertonicity may be ascribed to one or more of the following alterations:

- (1) reduced permeability of the distal tubule or collecting duct as a consequence of inadequate formation of ADH or inadequate responsiveness to ADH, or because of a primary alteration within the tubular membrane;
- (2) increased rate of solute flow (osmotic diuresis) by decreasing the effectiveness of the counter current multiplier, by enhancing the degree of dilution in the proximal portion of the distal tubule, and by limiting the ultimate concentration of the urine and of the medulla;
- (3) decreased solute concentration within the medulla because of (a) reduced capacity of the counter current multiplier to transport solute or (b) failure of the medullary circulation to trap the solute deposited therein.

The prompt response to a water load and to the subsequent administration of hyperosmolar solutions in our subjects indicates that the osmoreceptor-pituitary cycle operates normally. The return of urine osmolality toward pre-hydration levels after the administration of Pitressin indicates at least some enhancement of

tubular permeability to water. These data and interpretations are in accord with studies performed in patients with sicklemia by previous investigators [9-11].

The failure of the patients with sickle cell disease to augment the concentration of urine after the rate of flow down the tubule is diminished by decreasing the filtration rate argues against the alternative hypothesis of a reduced tubular permeability to water. The similarity in response to a diminished filtered load of the sickle cell and normal hydropenic subject (the latter presumably possesses tubules of maximum permeability to water) also suggests a normal permeability in the sickle cell subject. In subjects whose tubular permeability to water was reduced by the presence of diabetes insipidus or sustained water loads, similar stimuli have been reported to produce an abrupt increase in urine osmolality [31,36,37].

In those experiments in which the rate of solute flow was increased by a mannitol load, no evidence of urine hypo-osmolality or distal tubular impermeability to water was unmasked, such as was demonstrated in similar experiments recorded by de Wardener and Del Greco in patients with diabetes insipidus (Fig. 3) [38]. Furthermore, the slow rate of decrease in concentration of the urine and the persistence of some urine hypertonicity despite progressive increases in the rate of solute flow to levels exceeding 20 per cent of the filtered load argue against any (measurable) decrease in tubular permeability to water in the collecting ducts.

These series of experiments therefore provide convincing albeit indirect evidence that the permeability to water within the tubules remains normal in sickle cell subjects.

The control rates of solute excretion, in relation to the filtration rates in sickle cell subjects, are closely comparable to those observed in normal subjects. (Tables III and IV.) This finding tends to eliminate the possibility that an osmotic diuresis may have played a role in the isosthenuria of sickle cell subjects. Furthermore, in hydropenic subjects in whom a solute diuresis limits the concentration of the urine, a fall in glomerular filtration rate has been shown to produce a rise in urine osmolality [19,39].

By exclusion, it thus seems most likely that the isosthenuria of sicklemia reflects failure to achieve a normal medullary solute concentration. As already mentioned, the decreased concentration might be ascribed to a reduced

capacity of the ascending loop of Henle to transport sodium. However, no defect in overall sodium transport, as evidenced by a high control rate of salt excretion in relation to the glomerular filtration rate, was evident in these subjects. (Tables III and IV.) Furthermore, under conditions of maximum water loading, a marked dilution of the urine was achieved (Table II, Fig. 1), suggesting a normal capacity to absorb salt within the loop of Henle and distal tubule. While failure to accomplish this last could be obscured by an increased rate of salt absorption in the remainder of the distal tubule (thereby maintaining a normal over-all rate of salt excretion), it is probable that with increasing mannitol loads any diminished sodium transport would be unmasked. It will be noted that the increment in the rate of chloride excretion in the mannitol-loaded sickle cell subjects (Table IV) was of the same order as that produced by a comparable load in the normal subjects. When the glomerular filtration rate was reduced, salt excretion in the sickle cell subject fell to the same degree as in the normal subject. (Table III.) These data do not support the possibility of a defect in sodium or chloride transport in sicklemia.

It has been suggested that the efficiency of the countercurrent multiplier in the loop of Henle depends upon the permeability of the descending loop to water, making it possible for the concentration to rise progressively as the fluid descends this segment of the loop. That this is not the site of the defect in the sickle cell subject is suggested by the failure of the urinary concentration to rise as the rate of solute flow is decreased. As in other areas of impermeability to water, one would expect an increase in relative permeability with a slower rate of flow. Insofar as these experiments did not reveal any abnormality in the countercurrent multiplier, the postulated diminished medullary hypertonicity in sicklemia may be ascribed to the failure of the circulation to trap the solute deposited in the medulla.

The fall in urine osmolality produced by a decrease in glomerular filtration rate in hydropenic subjects has been attributed to the reduced quantity of urea available for back diffusion at the collecting duct [19,39]. The proportionately similar fall in total urine osmolality in sickle cell and normal subjects exposed to a comparable drop in glomerular filtration rate (Tables III and IV, Fig. 2) would suggest that, of the total solute in the medulla of the former, the proportion

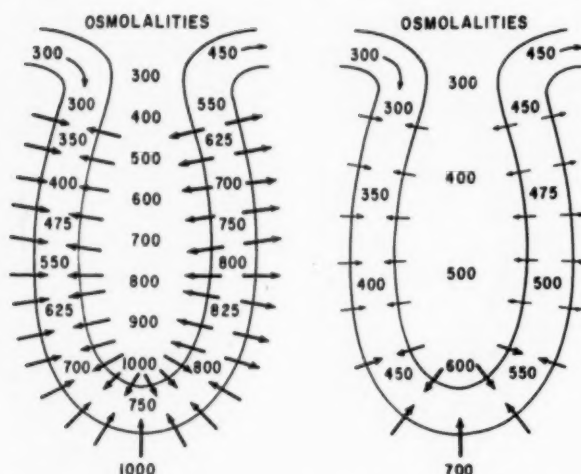


FIG. 5. A schematic presentation of the hypothetical defect in the medullary circulation of the sickle cell subject. *Left*, in the normal countercurrent circulation, the solute entering the tip freely diffuses out of the efferent loop and then diffuses into the afferent segment, causing the solute concentration to rise progressively as the blood approaches the apex. *Right*, in the sickle cell subject, it is hypothesized that far less solute diffuses out of the less permeable efferent segment. Accordingly the fall in concentration from the apex outward will be less marked, and less solute will be available for diffusion into the descending segment; consequently only a slight rise in solute concentration will occur as the blood approaches the pyramid.

representing urea is similar to that in the normal subject. This also would favor the hypothesis that solute enters this site normally in the sickle cell subject but does not remain there because of an alteration in the trapping characteristics of the circulation.

This hypothesis would, in addition, explain the slight fall in urine osmolality in the sickle cell subject as compared to the more pronounced fall in the normal subject when the rate of solute excretion increases. (Table IV, Figs. 3 and 4.) Normally, as the rate of urine flow increases, the medullary concentration falls as a result of the diluting effect of the increased quantities of water diffusing back [27,34]. If, as suggested, the medullary circulation of the sickle cell subject is a less efficient trap and therefore more effective in removing solute and water, the influence of an increased water load on medullary concentration would be less conspicuous than in normal subjects.

The precise nature of the abnormality as a result of which the countercurrent circulation in the sickle cell subject undergoes this change in function is not certain. The presence of prolonged arterial oxygen unsaturation in the sickle cell

subject has been substantiated [17,18]. It seems reasonable to assume that the degree of anoxia may be most marked in the efferent loop of the capillary circulation. If there is a high concentration of red cells within the medulla (contrary to the views of Pappenheimer), sickling of the red cells may be most conspicuous at this segment of the loop. Small vascular occlusions might then occur, causing the exudation of interstitial fluid proximal to this site. While such morphologic alterations have indeed been described in the medulla of such subjects [40,41], it is difficult to explain the reduced medullary tonicity on this basis alone. Even though an increased interstitial volume would limit the diffusion of solute and water across the vascular loops, it must be remembered that, according to the present hypothesis, solute is deposited in the interstices of the medulla. The presence of edema would probably limit the diffusion of solute into the capillaries, thereby tending to enhance the concentration within the medulla. If the prolonged anoxia caused a generalized reduction in permeability of the capillary wall, solute deposited within the interstitial fluid would not readily gain access to the capillary circulation, thus tending to increase the medullary concentration.

Prolonged anoxia in this capillary system could reduce the trapping effect of the circulation by permitting solute to enter the circulation freely, but limiting its re-diffusion from efferent to afferent loop. Figure 5 presents a schematic representation of how such an alteration in permeability of one segment of the capillary wall would markedly limit the trapping characteristics of the medullary circulation. It seems reasonable to assume that any alteration in permeability would occur most prominently in the efferent loop—that segment exposed to the more pronounced degree of anoxia over the years. Solute which had entered the descending limb and the apex of the capillary loop would not readily diffuse out of the ascending limb. Accordingly, less solute would be available for re-diffusion into the descending limb and a much smaller rise in solute concentration would develop as the blood in the vasa rectae approached the apex of the loop. Such a change would reduce the efficiency of the countercurrent system and in a physiologic sense tend to straighten the capillary loop, thereby increasing the effective medullary blood flow. This hypothesis is in accord with what has previously

been described as a "heaping-up" of endothelial layers in the loops of the capillaries [40]. It would be consistent with the fact that young sickle cell subjects elaborate a concentrated urine for some time after the infusion of normal red cells [17]; presumably before the effects of prolonged anoxia become irreversible the infusion of normal blood would reduce the anoxia and overcome the diffusion defect in the efferent loop, whereas in adults with irreversible changes the infusion of fresh blood would not reverse the effects of the endothelial changes in the capillary wall. This concept is in accord with the observation that dogs exposed to long-term anoxia exhibit a reduced capacity to concentrate the urine [42]. However, in several observations made in this laboratory no defect in maximum urine osmolality was noted in patients with prolonged anoxia of diverse etiology [43].

Infarction of the medulla has been described in subjects with sickle cell disease [41] but it is difficult to understand how the concentrating defect can be ascribed to this vascular change. For one thing, many isosthenuric sickle cell subjects show no evidence of renal infarction. Furthermore, as has been previously emphasized, a reduced medullary blood flow would not tend to reduce medullary tonicity but would instead exaggerate the trapping of solute. If such medullary ischemia interfered with the active transport of sodium, it might conceivably limit the concentration of salt in the medulla but the evidence presented herein offers no support for the presence of a defect in sodium transport in sickle cell subjects. Finally, it would be difficult to explain the transient improvement in concentration ability in young children infused with fresh blood on the basis of medullary infarctions.

SUMMARY AND CONCLUSIONS

1. The previous literature regarding the renal concentrating defect in subjects with sickle cell disease or sickle cell trait is briefly reviewed.

2. Experiments performed in such subjects demonstrated some responsiveness to the administration of Pitressin.

3. After the filtration rate was reduced in sickle cell subjects, under conditions of maximum hydropenia, urine osmolality decreased approximately 12 per cent. Similar experiments in normal control subjects revealed a comparable percentile fall in urine osmolality.

4. Osmotic loading in hydropenic sickle cell subjects caused a slow and slight decrease in

urine osmolality, the urine remaining hypertonic to plasma even at levels of solute excretion exceeding 20 per cent of that filtered.

5. The previous literature and the present findings are interpreted in terms of the current concept of the concentrating operation in the kidney.

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The Lungs in Rheumatoid Spondylitis*

Gas Exchange and Lung Mechanics in a Form of Restrictive Pulmonary Disease

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THE observation that rheumatoid spondylitis produces restriction of chest motion is at least 250 years old [7], and the disease is known to have existed since early times [2]. Pulmonary function tests now make possible documentation of this early observation and differentiation from other forms of restrictive pulmonary disease. We will describe the respiratory function of sixteen patients with rheumatoid spondylitis and discuss the form of pulmonary restriction with hyperinflation which they represent.

METHODS

Selection of Subjects and Preliminary Examination. Dr. T. B. Bayles of the Robert Breck Brigham Hospital selected sixteen patients for study (fifteen were men) who met the clinical and radiographic criteria for the diagnosis of rheumatoid spondylitis. Beyond their willingness to undergo the tests, no further requirement was exercised. No attempt was made, for example, to include or exclude patients with respiratory symptoms or other diseases. Patients were interviewed and examined. Height and weight were measured. Body surface area was estimated from the diagram of Sendroy and Cecchini [3].

Eleven healthy male subjects were selected from the medical housestaff for comparative study of minute volume, alveolar carbon dioxide tension (P_{ACO_2}) and oxygen consumption (\dot{V}_{O_2}).

Pulmonary Function Studies. With the patient sitting,

two determinations of maximum breathing capacity, vital capacity and one-second timed vital capacity were made using a Collins 9-L. respirometer. The larger of the values for vital capacity and maximum breathing capacity was used throughout. Duplicate measurements of functional residual capacity and residual volume were made by the closed circuit helium technic [4], using helium in air; the average value is reported. Total lung capacity is reported as the sum of vital capacity and residual volume. The "over-all" mixing index was calculated from the helium dilution curve by Gilson and Hugh-Jones' modification [5] of the method of Bates and Christie [6]. Expected values for maximum breathing capacity, vital capacity, total lung capacity and residual volume based on age, height, body surface area and sex were calculated from the equations of Baldwin, Cournand and Richards [7]. Comparison of these figures with our observed values is not strictly valid since Baldwin et al. studied their subjects in the supine position for lung volume and standing for maximum breathing capacity, whereas our subjects were seated for all procedures. Predicted volumes for functional residual capacity were calculated from the normal figures for percentage of total lung capacity given by Kaltreider, Fray and Hyde [8].

Lung compliance and total flow resistance were measured in thirteen of the patients. Simultaneous measurements of lung volume change and intraesophageal pressure change (as an index of intrapleural pressure) during spontaneous quiet respiration allowed calculation of lung compliance and air and tissue flow resistance [9]. An intraesophageal

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balloon similar to that described by Mead *et al.* [10] was used. The data from these patients were compared to similar studies by Frank and co-workers in healthy young and elderly persons [11,12]. The results for the patients who had pulmonary disease besides spondylitis are not included in the calculated averages. Maximum inspiratory and expiratory airway pressures were measured (beginning at the maximum expiratory and inspiratory positions, respectively) with an aneroid manometer attached to a mouthpiece with a high grade obstruction.

Measurements of minute volume of ventilation, \dot{V}_{O_2} and P_{ACO_2} were made during quiet breathing after the patient had rested in a chair for fifteen minutes. The values were compared with those of eleven healthy subjects studied in our laboratory. For measurement of carbon monoxide diffusing capacity of the lung (D_{LCO}) the following additional procedure was carried out. An indwelling needle was placed in the brachial artery. A sample of blood for O_2 analysis was taken prior to the CO inhalation. The D_{LCO} was then measured by the steady state method of Filley, MacIntosh and Wright [13] as modified by Marks *et al.* [14]. This consists of a seven minute period of inhalation of 0.1 per cent CO (in air) and collection of expired gas into a well washed Douglas bag during the last four minutes of this period. There was continuous sampling of air from the respiratory valve through a Beckman infra-red CO_2 analyzer with microcatheter cell (for measurement of end-tidal P_{CO_2}) into the Douglas bag. During the four-minute period of gas collection, arterial blood was drawn and promptly analyzed for CO_2 content and pH. Expired gas was analyzed for CO_2 and O_2 by the Scholander one-half cubic centimeter method [15]. The CO concentration of expired air was measured with a Beckman infra-red CO meter. No correction was made for the influence of carbon dioxide on the infra-red CO analyzer. Arterial CO tension was not measured. Gas volumes were measured in a Tissot spirometer, and correction was made for the volumes used in analysis. Alveolar oxygen tension (P_{AO_2}) was calculated by the alveolar air equation.

Blood pH was measured with a Beckman Model G meter at room temperature and corrected to 37°C. by the factors of Rosenthal [16]. Carbon dioxide and O_2 content and O_2 capacity were measured by the manometric method of Van Slyke and Neill [17]. Plasma CO_2 content was calculated from the whole blood CO_2 content by correction factors involving hematocrit [18]. Carbon dioxide tension was calculated by the Henderson-Hasselbalch equation.

RESULTS

History, Physical Examination, and Roentgenograms of the Chest. A summary of pertinent clinical findings is given in Table 1.

Half of the patients reported that, on coughing and sneezing, they experienced thoracic discomfort. This was described in various ways: a tight feeling in the chest, a pressure in the upper anterior thorax, an exaggeration of a persistent ache between the shoulder blades, or a distressing, bone-shaking pain particularly severe upon sneezing. Only one patient (Case 2) experienced chest pain during pulmonary studies.

In Cases 9 and 16 mild dyspnea on exertion was reported; two patients (Cases 12 and 13) had severe, disabling dyspnea. In Case 12 rheumatic heart disease with predominant mitral valvular disease was apparent. In Case 13 there was marked pulmonary emphysema. The remaining twelve patients gave no history of dyspnea, but in ten cases arthritis limits their activity.

Six patients (Cases 1, 3, 6, 13, 15, 16), all of whom were heavy cigarette smokers, had a chronic cough, usually with little sputum. In Case 6 four episodes of pneumonia and one of influenza within the past ten years was reported. In Case 13 a history of two episodes of pneumonia within the past six years was given. Ten patients had no history of acute pulmonary infections.

All sixteen patients had immobility of the spine and markedly impaired mobility of the bony thorax. Posture had been maintained sufficiently erect to permit vision straight ahead, and in twelve of the patients (all except Cases 1, 6, 12, 13) orthopedic treatment, consisting of exercises or casts, had achieved ankylosis of the spine in a position with a straightened dorsal curvature. In Case 12 residual scoliosis following a spinal fusion for collapse of a thoracic vertebra occurred. In Case 14 (who was seventy-four years old) there was mild pectus excavatum and osteoarthritis of the spine. Two patients had cyanosis; in Case 13 cyanosis occurred as a result of chronic pulmonary disease, and in Case 6 as a result of an apparently unrelated condition, hemoglobin M disease. Clubbing of the fingers was not found. Breathing was largely diaphragmatic, the chest wall expanding little with effort (less than 3 cm. in circumference at the nipple line in all patients). Peripheral joint involvement was present in three patients. In Case 5 there was psoriasis with marked exfoliation. A faint aortic diastolic murmur was heard in one patient (Case 15), but this was of no apparent hemodynamic significance.

Roentgenograms of the chest are summarized

TABLE I
CLINICAL DATA OF SIXTEEN PATIENTS WITH RHEUMATOID SPONDYLITIS

Case No.	Age (yr.) and Sex	Reported Duration of Symptoms (yr.)	Roentgenogram of the Chest	History of Chest Pain on Sneezing or Coughing	History and Physical Findings in Addition to Rheumatoid Spondylitis
<i>Patients with Rheumatoid Spondylitis</i>					
1	49, M	10	Increased markings	0	Heavy smoker, chronic cough; gastric ulcer; peripheral arthritis
2	20, M	6	Clear	+	Mild anemia
3	45, M	26	Clear	0	Heavy smoker, dry cough; one attack of iritis
4	42, M	14	Clear	+	Active mountain climber; asymptomatic
5	51, M	40	Clear	0	Large sthenic build; psoriasis with generalized exfoliation; one attack of iritis; peripheral joint involvement
6	58, M	18	Clear	0	Heavy smoker, chronic bronchitis, four episodes of pneumonia and one of influenza during past ten years; chocolate blue lips; methemoglobin M
7	23, M	7	Clear (at time of studies)	+	Right apical infiltration of lung 5 months before study; treatment with isoniazid and paraminosalicylic acid
8	41, M	16	Clear	0	Mild smoker, no cough; four attacks of iritis
9	47, M	2	Increased markings	+	Heavy smoker; mild dyspnea on exertion; pneumonia at age 3
10	41, M	1½	Clear	+	Syphilis, treated 20 years previously; one brother, rheumatoid spondylitis; one brother, rheumatoid arthritis; one attack of iritis
11	43, M	3	Clear	+	Treated with cortisone during preceding 3 years
<i>Patients with Rheumatoid Spondylitis and Complicating Diseases</i>					
12	48, F	29	Prominent pulmonary artery	+	Chorea at age 12; rheumatic fever at age 19; history of gastric ulcer; fusion of spine after aseptic necrosis of dorsal vertebra, residual scoliosis; one attack of iritis; findings of rheumatic heart disease with mitral stenosis, mitral and aortic insufficiency; peripheral arthritis
13	52, M	22	Marked increase in radiolucence of lung fields; low, flat diaphragm	0	Heavy smoker; chronic cough; bronchopneumonia twice in past 6 years; severe dyspnea on exertion; cyanosis
14	74, M	12	Increased radiolucence of lung fields, low diaphragm	0	Pectus excavatum, mild; osteoarthritis of spine; attack of iritis at age 24; attack of sciatica at age 34
15	47, M	7	Infiltration in left upper lobe and left lower lung field, pleural thickening right apex	+	Mild smoker; chronic cough with little sputum; faint diastolic murmur at left sternal border probably of no hemodynamic significance; lung lesions were found on routine chest roentgenogram after respiratory studies were completed
16	47, M	14	Increased markings, low diaphragm	0	Heavy smoker, chronic bronchitis, heavy colds with persistent cough; influenza 2½ months before study; cleft palate; pneumonia in 1935

in Table I. In seven patients (Cases 2, 3, 4, 5, 8, 10 and 11) lung fields were clear. Between episodes of pneumonia the lungs of one patient (Case 6) appeared normal. Two patients (Cases

1 and 9) had increased markings of the lungs. In Case 7 a small apical lesion was discovered on initial examination, but five months later, at the time of the reported studies, the lungs were

TABLE II
VENTILATION DATA

Case No.*	Age (yr.) and Sex	Maximum Breathing Capacity (L./min.)		One Second Vital Capacity (% of total)	Vital Capacity (L.)		Functional Residual Capacity (L.)		Residual Volume (L.)		Total Lung Capacity (L.)		Ratio of Residual Volume/ Total Lung Capacity (%)	Over-all Mixing Index (%)
		Observed	Predicted		Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted		
Patients with Rheumatoid Spondylitis														
1	49, M	67	99	64	1.71	3.34	1.49	1.66	1.29	1.08	3.00	4.60	42	40.6
2	20, M	102	138	100	2.78	4.42	2.95	2.10	2.00	1.16	4.78	5.80	43	47.5
3	45, M	120	103	95	2.73	3.84	3.95	1.92	2.93	1.25	5.66	5.32	51	67.2
4	42, M	105	123	100	2.76	4.08	4.10	2.01	2.71	1.31	5.47	5.59	48	44.2
5	51, M	102	134	73	2.76	3.95	6.72	2.70	5.59	2.05	8.35	6.65	66	45.3
6	58, M	78	96	70	2.84	3.51	5.15	2.17	3.86	1.65	6.70	5.35	59	23.6
7	23, M	116	129	96	2.75	4.21	3.49	1.99	2.57	1.10	5.32	5.50	54	46.0
8	41, M	127	110	100	2.98	3.71	2.50	1.84	1.50	2.20	4.48	5.10	33	53.7
9	47, M	113	107	78	3.43	3.80	5.99	1.80	2.40	1.00	5.83	5.00	42	...
10	41, M	64	128	44	3.58	4.17	4.18	2.07	2.67	1.34	6.25	5.74	43	44.3
11	43, M	55	109	66	2.25	3.81	4.14	1.88	3.03	1.22	5.28	5.22	57	47.7
Mean	41.8	95	116	80	2.78	3.89	4.06	2.01	2.78	1.40	5.56	5.44	49	46.0
Standard error of the mean		±7.5	±4.5	±6	±0.15	±0.10	±0.45	±0.08	±0.43	±0.12	±0.41	±0.16	±3	±3.4
Patients with Rheumatoid Spondylitis and Complicating Diseases														
12	48, F	32	68	85	1.23	2.51	2.20	1.17	1.72	0.76	2.95	3.27	59	28.0
13	52, M	83	84	100	1.28	3.49	4.92	1.81	4.23	1.55	5.51	5.04	75	10.5
14	74, M	124	81	83	2.76	3.31	4.35	1.81	2.88	1.55	5.64	5.03	50	45.7
15	47, M	116	109	84	3.15	3.80	4.01	1.88	2.55	1.22	5.70	5.22	45	46.5
16	47, M	69	96	61	2.17	3.67	3.06	1.81	2.35	1.18	4.52	5.04	53	40.0

* Height, weight, body surface area are given in Table III.

clear. In Case 12 (the only woman and the only patient with rheumatic heart disease) a prominent pulmonary artery but clear lung fields was apparent. In Cases 13 and 14 there were low, flat diaphragms and areas of increased radiolucence. In Case 15 extensive areas of infiltration in the left upper lobe and in the left lower lung field were found. In Case 16 there were increased markings in the lung fields and low diaphragm.

Pulmonary Function Studies. The data from studies in Cases 1 through 11 are presented in Tables II, III and IV and illustrate the effects of rheumatoid spondylitis on respiratory function when a minimum of complicating factors are present. Five cases (Cases 12, 13, 14, 15 and 16) are tabulated separately in the tables because factors, in addition to rheumatoid spondylitis, exist in these patients which make it difficult to assess the role of spondylitis *per se*. These additional factors are rheumatic heart disease with congestive heart failure (Case 12), severe pulmonary emphysema (Case 13), mild emphysema (Case 16), senile emphysema, pectus excavatum and osteoarthritis of the spine (Case

14), and pulmonary tuberculosis with extensive infiltrations in the left lung (Case 15). These five patients are excluded from averages given in the text and tables and from comparisons with healthy subjects. It is not possible strictly to exclude additional pulmonary disease from the first eleven patients, since three patients (Cases 1, 2 and 6) were heavy smokers with a chronic cough. In Table II the maximum breathing capacity, lung volumes and the over-all mixing index are given for sixteen patients. In Table III the data on minute volume, \dot{V}_{O_2} , and P_{ACO_2} for sixteen patients and eleven healthy subjects are given with calculated figures of ventilatory equivalent and alveolar ventilation. The data on mechanics of breathing in thirteen patients appear in Table IV.

Vital capacity in Cases 1 to 11 was consistently reduced. By the t test the mean for the group was significantly ($P = <0.001$) below the value calculated from the formula of Baldwin *et al.* [7]. The fact that our subjects were seated and those of Baldwin *et al.* were supine does not alter the significance of this difference [19]. Our patients

TABLE III
VENTILATION AND ARTERIAL BLOOD VALUES
(PATIENTS SITTING AT REST, AWAKE, BREATHING AMBIENT AIR)

Case No.	Age (yr. and Sex)	Height (cm.)	Weight (kg.)	Body Surface Area (M ²)	Ventilation (L./min./M ²)	Ventilation Equivalent (L./100 ml. O ₂)	Alveolar Ventilation (L./min./M ²)	O ₂ Uptake (ml./min./M ²)	Respira- tory Exchange Ratio	Calculated Alveolar O ₂ Tension (mm. Hg)	End-Tidal "Alveolar" CO ₂ Tension (mm. Hg)	Arterial Blood		Steady State Diffusing Capacity of Lung for CO (ml./min./mm. Hg)	
												CO ₂ Tension (mm. Hg)	pH		O ₂ Satura- tion (%)
Patients with Rheumatoid Spondylitis															
1	49, M	151	61.2	1.63	2.37	39.0
2	20, M	174	69.4	1.82	3.21	2.14	2.37	150	0.87	96.8	43.5	36.2*	7.44	98	21.9
3	45, M	170	56.4	1.64	5.01	2.91	3.36	172	0.84	108.9	37.5	38.6	7.44	99	30.2
4	42, M	178	74.1	1.90	3.18	2.36	2.74	134	0.76	94.4	45.5	41.6*	7.45	94	...
5	51, M	180	97.6	2.16	4.54	...	3.31	43.2
6	58, M	166	63.8	1.71	4.16	2.78	2.19	149	0.75	93.0	44.5	44.8	7.49
7	23, M	168	66.2	1.73	4.40	2.24	3.09	196	0.70	92.5	40.3	40.9	7.42	98	11.6
8	41, M	161	64.5	1.69	2.59	2.23	1.84	116	0.82	99.7	42.0	34.3*	7.42	90	10.0
9	47, M	170	63.5	1.72	4.98	3.02	3.53	164	0.92	108.8	37.4	37.4	7.46	97	11.4
10	41, M	181	78.0	1.97	3.68	2.56	2.55	143	0.87	102.4	42.3	42.4	7.40	93	22.0
11	43, M	167	62.0	1.70	3.86	2.48	2.84	155	0.83	99.4	43.2
Mean	41.8	169	68.8	1.79	3.96	2.52	2.78	153	0.82	99.5	41.8	39.5	7.44	96	16.6
Standard error of the mean	±2.6	±3.4	±0.05	±0.11	±0.25	±0.11	±0.17	±7.5	±0.02	±2.1	±0.8
Patients with Rheumatoid Spondylitis and Complicating Diseases															
12	48, F	148	49.1	1.41	4.26	...	2.94	42.5
13	52, M	160	44.5	1.42	7.34	4.27	2.88	172	0.72	99.0	31.4	38.3	7.43	89	...
14	74, M	171	60.5	1.69	4.33	2.52	2.56	172	0.82	90.7	49.2	51.8	7.36	98	18.5
15	47, M	170	67.0	1.76	2.98	2.76	1.70	108	0.71	96.5	39.8	38.5	7.46	96	...
16	47, M	164	52.7	1.55	4.86	2.69	2.80	180	0.70	101.7	39.3	39.5	7.43	98	7.0
Healthy Subjects															
E. R.	38, M	168	88.0	2.01	3.71	2.78	2.98	133	0.85	109.4	34.2
D. J.	31, M	177	67.0	1.79	4.14	2.77	2.46	150	0.78	96.4	42.5
D. Z.	24, M	185	92.1	2.14	4.77	2.84	3.90	168	0.99	110.0	39.0
S. W.	25, M	175	68.6	1.80	3.37	2.24	2.76	150	0.85	102.5	41.0
D. T.	31, M	206	101.4	2.35	4.16	2.97	2.56	140	0.78	102.5	38.3
J. C.	27, M	191	85.0	2.09	4.22	2.43	3.41	173	0.81	105.5	36.7
D. B.	25, M	174	69.5	1.82	4.53	2.93	3.52	155	0.90	112.3	33.9
R. F.	27, M	188	83.0	2.05	3.18	2.09	2.10	152	0.67	89.2	43.0
E. B.	60, M	171	76.4	1.86	4.31	3.18	2.99	135	0.97	111.0	37.3
G. H.	26, M	180	75.1	1.90	4.66	2.25	3.22	207	0.72	95.4	41.3
P. B.	27, M	182	86.1	2.05	2.73	2.18	2.00	125	0.74	96.2	44.6
Mean	31	182	81.1	1.99	3.98	2.61	2.90	153	0.82	102.8	39.3
Standard error of mean	±3.2	±3.3	±0.05	±0.11	±0.69	±0.11	±0.18	±6.8	±0.10	±7.5	±1.1

* Indicates probable error.

TABLE IV
MECHANICS OF BREATHING

Case No.	Age (yr.)	Compliance (ml./cm. H ₂ O)		Airway Resistance (cm. H ₂ O/L./sec.)	End-Expiratory Transpulmonary Pressure (cm. H ₂ O)	Maximum Static Inspiratory Transpulmonary Pressure (cm. H ₂ O)	Maximum Positive Airway Pressure (cm. H ₂ O)
		Observed	Predicted*				
Patients with Rheumatoid Spondylitis							
1	50	0.196	0.097	2.9	1.9	14.3	...
2	22	0.120	0.172	4.0	6.9	21.0	...
3	45
4	43	0.118	0.191	1.6	6.3	17.2	95
5	51
6	58	0.121	0.148	3.5	4.5
7	23	0.116	0.150	1.5	5.8
8	42	0.121	0.131	2.5	5.6	24.1	143
9	48	0.174	0.162	1.9	2.6	19.2	85
10	42	0.166	0.200	2.4	2.9	20.2	125
11	44	0.129	0.152	1.9	1.5	17.6	147
Patients with Rheumatoid Spondylitis and Complicating Diseases							
12	48
13	52	0.067	0.124	2.9
14	75	0.119	0.155	2.2	3.9	10.6	...
15	48	0.101	0.162	1.8	9.1	36.0	164
16	48	0.135	0.142	2.6	5.1	17.0	...
Mean for Six Youngest Patients†							
	36	0.128	0.166	2.3	4.6	20.0	...

* Calculation of predicted value is by the formula:

$$(0.00343 \times \text{height}) - 0.425 \text{ (younger)} \quad \text{or} \quad (0.00343 \times \text{height}) - 0.421 \text{ (older)}$$

† Cases 2, 4, 7, 8, 10 and 11. Average height = 171.5 cm.

did not have a reduction of vital capacity much below about 50 per cent without evident disease in addition to spondylitis. Typically, two patients (Cases 12 and 13), who had the lowest absolute and relative values of vital capacity, had severe additional disease.

The mean one-second vital capacity in Cases 1 to 11 was 79 per cent of the total vital capacity (the identical mean value of healthy persons in our laboratory), but there was a greater range (44 to 100 per cent) than we usually see in normal subjects (71 to 86 per cent).

The mean maximum breathing capacity of the eleven patients was significantly lower ($P = <0.05$) by the *t* test than the mean values

calculated for these patients from the formula of Baldwin et al., although three patients had normal values.

Calculation of the air velocity index (per cent of predicted maximum breathing capacity divided by per cent of predicted vital capacity) in Cases 1 to 11 gives a mean of 1.18 which is significantly higher ($P = <0.02$) than the mean of 0.99 for healthy subjects studied in our laboratory.

For these eleven patients the mean total lung capacity was approximately the same as the expected value. Residual volume was significantly higher ($P = <0.005$) than the mean value predicted. This results in a high mean ratio residual volume/total lung capacity of

49 per cent compared to the figure of 23.4 per cent found by Kaltreider *et al.* for age group thirty-eight to fifty years [8]. The mean expiratory reserve volume fraction of vital capacity (figures not given in the tables) was only slightly larger (41 per cent of observed vital capacity) than the normal value of 34 per cent found by Whitfield *et al.* in the sitting position [19]. Functional residual capacity was considerably larger than predicted ($P = <0.001$), reflecting the absolute increases in residual volume and expiratory reserve volume. Intrapulmonary gas mixing, expressed as the over-all mixing index was above 40 per cent in all but one of Cases 1 to 11, with a mean of 46 per cent. This is well above the range of 11.5 to 37 per cent mixing efficiency estimated by Bates and Christie in a group of twenty patients with emphysema [6], and comparable to normal values found by Gilson and Hugh-Jones [5]. Additional evidence of normal mixing can be seen in the close agreement between end-tidal "alveolar" P_{CO_2} and the arterial P_{CO_2} in five patients. This stands in contrast to one patient (Case 13), with severe emphysema, who had an arterial-alveolar P_{CO_2} difference of 7 mm. Hg, indicating an uneven ventilation-perfusion relationship.

Steady state $D_{L_{CO}}$ was measured in eight patients. The mean of values from six patients in the uncomplicated group was 16.6 ml./min./mm. Hg, which is not significantly different from the mean of 19.5 ml./min./mm. Hg found by Marks *et al.* [14].

Minute volume, \dot{V}_{O_2} , P_{ACO_2} and calculations of alveolar ventilation, ventilatory equivalent, respiratory exchange ratio and P_{AO_2} of the eleven patients are compared with corresponding values for eleven healthy subjects in Table III. There are no significant differences in mean values for the two groups. It may be seen that in two patients (Cases 4 and 6) there was a P_{ACO_2} above 44 mm. Hg. Among those patients in whom spondylitis was complicated by other disease, one patient (Case 14) had a high arterial P_{CO_2} of 51.8 mm. Hg.

Arterial P_{CO_2} , measured in thirteen patients, compared closely (within 3 mm. Hg) with the end-tidal values except in three patients in whom the arterial value was 3 mm. Hg lower than the alveolar values. In these three patients the arterial value is assumed to be a technical error. Only one arterial hemoglobin O_2 saturation was definitely low (90 per cent in Case 8)

without evidence of pulmonary disease in addition to spondylitis.

The results of the measurements of lung compliance, tissue and air flow resistance, transpulmonary pressures, and maximal expiratory airway pressures are given in Table IV. The eleven patients without primary respiratory disease have been separated from the five patients with emphysema or complicating diseases of the lung. The predicted values for compliance were estimated from the data of Frank *et al.* for young [17] and elderly [12] adults. Because of the lack of adequate control data for persons between forty-five and sixty-five years of age, only the data from six subjects forty-four years and under (average age thirty-six years) have been included in the averages used for comparison. In all but two of the nine patients who had no complicating pulmonary disease, the lung compliance was significantly lower ($P = <0.01$) than predicted. Similarly, if the data from the six younger patients are compared to the subjects (averaging thirty-four years of age) reported on by Frank [17], there is also a significant ($P = <0.01$) reduction in lung compliance.

End-expiratory transpulmonary pressures taken at rest for these same six patients are similar to those reported by Frank (4.6 cm. H_2O versus 4.2) [12]. However, the maximum static inspiratory transpulmonary pressure is significantly ($P = <0.01$) reduced in those patients with spondylitis (20.0 cm. H_2O versus 30.4).

Measurements of tissue and air flow resistance of the eleven patients with spondylitis uncomplicated by primary pulmonary disease were, with one exception, within the normal range averaging 2.3 cm. $H_2O/L./second$ versus 1.9 reported for younger and 2.8 for older normal adults [11,12].

Measurements in seven patients of maximum airway pressure on expiration and inspiration indicated significant reduction; average maximum expiratory pressure in these patients was 127 cm. H_2O versus approximately 200 cm. H_2O for controls; average maximum inspiratory pressure (data not included in table) was minus 51 cm. H_2O versus approximately minus 100 cm. H_2O for normal persons.

COMMENTS

Rheumatoid spondylitis is accompanied by restriction of the lung which is secondary to an immobile bony thorax, produced by ankylosis of the spine and costovertebral joints.

The form of restriction seen in the patients with uncomplicated rheumatoid spondylitis is unique. It differs from other reported forms of restrictive pulmonary disease in that the total lung capacity is normal rather than reduced. The vital capacity is reduced, not only because of limited expansion but also because of limited relaxation or contraction of the chest from a position of relative hyperinflation at rest. Flexion of the dorsal spine, a normal part of full expiration, is limited. In the present series the chest cage is fixed in an inflated position at rest, with a mean functional residual capacity twice normal. This hyperinflation is due to fixation of the chest in an expanded position, which is secondary, at least in part, to the orthopedic treatment resulting in flattening of the normal dorsal curvature.

In contrast to the present series, in those patients who have not had orthopedic management marked bowing of the dorsal spine often develops. The pathologic anatomy in such cases is described by Connor [7] and can be seen in a recent reprinting of his illustration [20]: "The direction of the ribs was unnatural, for instead of terminating at the sternum in parallel semi-circles nearly horizontal, their extremities, where they reached the sternum, dipped so much down towards the hypogastrium as to touch the sides of the ossa illii." With this decrease in intercostal spaces, the resulting diminished lung volume is apparent. Two patients (Cases 1 and 12) had the most marked dorsal curvatures of the spine, although none of our patients had the degree of bowing described by Connor.

Earlier reports on pulmonary function in rheumatoid spondylitis have included only a few with complete data on lung volumes. Rogan et al. [21] described a series of patients with decreased total lung capacity and vital capacity, the residual volume being normal. Girard and Renzetti et al. [22] found reduced total lung capacity and a small increase in residual volume. The present report stands in contrast to these previous studies in the finding of relatively normal total lung capacity and strikingly increased residual volume and functional residual capacity. The reasons for these differences are not apparent from the data given, although it is possible that the lower total lung capacity in these reports is due to differences in position of rib fixation.

The form of restrictive pulmonary disease described in the present paper is of great interest. The fact that the end-tidal transpulmonary pressures at rest are normal while the functional

residual capacity is considerably increased indicates that there has been a loss of elastic recoil within the lungs. However, although there is some resemblance to obstructive pulmonary emphysema (high residual volume, functional residual capacity, residual volume to total lung capacity ratio and altered elastic recoil of the lung), there are fundamental differences; in spondylitis there is normal intrapulmonary gas mixing, a normal ventilation-perfusion relationship, a restrictive pattern of breathing (per cent of predicted maximum breathing capacity divided by per cent of predicted vital capacity is significantly greater than normal), normal one-second vital capacity, normal flow resistance, no air trapping, and, finally, no progression to hypoxia, hypercapnia, or cor pulmonale. It would be of interest to compare the gross and microscopic pathologic findings in the lungs of patients with spondylitis to those with idiopathic emphysema.

In these patients with spondylitis a superficial resemblance to the changes in pulmonary function occurring in old age is apparent (decreased vital capacity, increased residual volume, increased residual volume to total lung capacity ratio, altered elastic recoil within the lung). However, essential differences are again noted: total lung capacity is consistently reduced with aging, whereas total lung capacity may be normal in spondylitis; functional residual capacity does not seem to change with age, whereas in treated spondylitis, it is increased [23]. Thus, the patients studied here illustrate another form of prolonged hyperinflation of the chest, occurring in young adults and apparently based on anatomical abnormalities of the thorax.

Lung compliance in the tidal range is significantly reduced in the patients with spondylitis. With the present data it is impossible to say whether this reduction represents an intrinsic change in the lungs or merely is the change which one might normally expect when the tidal range of respiration is shifted to a larger lung volume. In any case, this decreased compliance must contribute somewhat to an increased work of respiration.

The significant reduction in maximum static inspiratory transpulmonary pressures in spondylitis must be, at least in part, related to fixation of the chest cage and the inability of the diaphragm alone to produce normal maximal inspiratory pressures. Such a limitation in maximal transpulmonary pressures will not lead to respiratory embarrassment as long as activity

is limited, but might be critical with exertion. The reduced performance of maximum breathing capacity may be related to this limitation. The reduction in maximum positive and negative tracheal pressures represents a failure of the respiratory muscles to compensate for the abnormalities of the bony framework. The fixation of the ribs in an expanded position reduces the amount of potential intercostal muscle shortening for further inspiratory excursion. Whether or not the lack of exercise for these thoracic respiratory muscles, due to the patients' lack of activity, is a contributing factor in their inadequate performance is uncertain. It is possible that the reduction in maximum tracheal positive pressure may result in ineffective coughing and limit expectoration when the need arises. Cruickshank concurs [29b].

The clinical consequences of rheumatoid spondylitis related to respiration are worthy of attention. In the process of ankylosis the patient is aware that his thoracic viscera are being slowly encased in a rigid bony frame. The course may be a painful one, extraordinarily so on sneezing and coughing. Dyspnea is rather uncommon. Our impression that pulmonary infections and chronic lung failure are not necessarily more frequent in spondylitis is supported by the recent study of Wilkinson and Bywaters [24] showing no difference in incidence of pulmonary complication between 212 patients with ankylosing spondylitis and 253 patients with rheumatoid arthritis [25]. Earlier reports [26–29a] attempting to show a relationship between rheumatoid spondylitis and the development of pulmonary infections are based on clinical impressions and lack convincing comparative evidence.

The degree of restriction in rheumatoid spondylitis is usually insufficient to produce alveolar hypoventilation at least under resting conditions. Patients with uncomplicated spondylitis had a normal P_{ACO_2} . Occasionally higher values are seen, possibly due to additional factors. For example, in Case 14, a seventy-four year old retired army colonel, there was a high arterial P_{CO_2} of 51.8 mm. Hg on an initial study. When the studies were repeated four months later he had increased his resting minute ventilation by 30 per cent and lowered the arterial CO_2 tension by 7 mm. Hg. The reasons for this fluctuation are not clear. In a mild stepping exercise, one patient (Case 7) showed a rise in P_{ACO_2} of more than 5 mm. Hg. However, persistently elevated P_{ACO_2} at rest was not

seen. In fact, progressive pulmonary insufficiency seems to be uncommon in rheumatoid spondylitis.

In regard to the changes observed in vital capacity, it is apparent that there must be a limit to the reduction of vital capacity which can be produced by immobilization of the bony thorax alone. Strapping the chest reduces vital capacity by about 30 per cent [30]. It is unlikely that complete rigidity of the bony thorax would reduce vital capacity by much more than 45 per cent, assuming that expiratory reserve volume contributes about 34 per cent of the total vital capacity [79] in the sitting position. Once ankylosis and deformity of the spine is stabilized, the reduction of vital capacity becomes a static rather than a progressive abnormality.

SUMMARY

Sixteen patients with rheumatoid spondylitis are presented with studies of lung volumes, gas exchange and the mechanics of breathing, and are discussed as representing a form of restrictive pulmonary disease with hyperinflation of the resting chest cage. The restriction, and apparently also the hyperinflation, are the result of fixation of the chest in an expanded position by ankylosis of the spine and ribs. The majority of patients exhibited a relatively straight spine.

Eleven of the patients had no complicating cardiac or pulmonary diseases. In these the most significant changes were a reduction in vital capacity (70 per cent of predicted), a markedly increased residual volume and functional residual capacity, and a residual volume to total lung capacity ratio which averaged 49 per cent. In addition the elastic recoil of the lungs at resting mid-position was decreased. Although these findings resemble obstructive pulmonary emphysema, lung function was different in other respects: there were normal ventilation-perfusion relationships, normal intrapulmonary gas mixing, normal one-second vital capacity, normal flow resistance, no air trapping and a restrictive pattern of breathing. In addition, the total lung capacity was normal.

Other significant consequences of the immobilization of the thoracic cage were a diminution in the maximum static inspiratory transpulmonary pressure, diminished maximum positive and negative tracheal pressures, and a reduction in maximum breathing capacity.

Painful sneezing and coughing, abdominal breathing and absence of dyspnea are important clinical features of rheumatoid spondylitis.

The restrictive disease of rheumatoid spondylitis is usually not severe enough to produce alveolar hypoventilation. Pulmonary insufficiency and frequent pulmonary infections are not characteristic of uncomplicated rheumatoid spondylitis, indicating that diaphragmatic breathing is adequate to maintain normal pulmonary function, at least while activity is subdued.

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The Spatial Vectorcardiogram in Left Bundle Branch Block and Myocardial Infarction, with Autopsy Studies*

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IT is still widely accepted that myocardial infarction cannot be diagnosed in the presence of left bundle branch block. For theoretic reasons to be discussed later, the spatial vectorcardiogram should be helpful in the diagnosis of myocardial lesions, such as myocardial infarction, complicated by left bundle branch block. Accordingly, it was decided to review the vectorcardiographic records of patients with left bundle branch block to determine whether or not myocardial infarction could be detected in the presence of left bundle branch block from the spatial vectorcardiogram.

Seventy-seven spatial vectorcardiograms from patients with left bundle branch block were available for study; of these seventy-seven patients, twenty-four were autopsied. Fifteen of the autopsied patients were found to have myocardial infarctions. The study of the entire group of seventy-seven patients is the subject of another report [1]. The purpose of this paper is to present in detail the vectorcardiographic characteristics of left bundle branch block complicated by myocardial infarction for the fifteen patients whose hearts were studied at autopsy.

MATERIALS AND METHODS

The spatial vectorcardiograms were recorded as previously described, employing the equilateral tetrahedral reference system [2]. Photographic recordings of the various plane projections as well as wire loop models of all the spatial vectorcardiograms were studied. The routine conventionally recorded standard leads, unipolar limb leads and precordial leads V_1 to V_6 were also studied.

The fifteen patients ranged in age from thirty-three to seventy-two years with a mean of fifty-nine years. Ten were men and five were women; eleven were

white and four were Negro. The clinical and autopsy data are summarized in Table 1.

RESULTS

Before describing the configuration of the QRS $s\hat{E}$ -loop for left bundle branch block complicated by myocardial infarction, it may be well to review the spatial vectorcardiographic pattern of uncomplicated left bundle branch block and of left bundle branch block with left ventricular hypertrophy as found in this laboratory [1,3].

Uncomplicated Left Bundle Branch Block. Figure 1 shows the spatial vectorcardiogram and electrocardiogram of a fifty-seven year old woman who was without clinically significant heart disease. Her electrocardiogram displayed transitory left bundle branch block. During normal conduction (Fig. 1A) the electrocardiogram was normal, as was the spatial vectorcardiogram except for changes in the QRS $s\hat{E}$ -loop previously described for aging [4].

During the left bundle branch block (Fig. 1B) the QRS $s\hat{E}$ -loop was displaced horizontally and to the left, superiorly and posteriorly, and was inscribed slowly in a counterclockwise direction. The T $s\hat{E}$ -loop was displaced 180 degrees away from the QRS $s\hat{E}$ -loop and to the right, inferior and anterior to the isopotential point. The T $s\hat{E}$ -loop was not closed but was fused with the QRS $s\hat{E}$ -loop at the junction J which was to the right, inferior and anterior to the isopotential point. This displacement of the junction J in the spatial vectorcardiogram corresponds to the shift in the S-T segment noted in the electrocardiogram (Fig. 1B).

Left Bundle Branch Block with Left Ventricular Hypertrophy. Figure 2 shows the spatial vector-

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TABLE I
CLINICAL AND AUTOPSY DATA FOR FIFTEEN PATIENTS WITH LEFT BUNDLE BRANCH BLOCK AND MYOCARDIAL INFARCTION

Case No.	Age (yr.) and Sex	Race	Weight of Heart (gm.)	Thickness of		Myocardial Surface Involved
				Left Ventricle (cm.)	Right Ventricle (cm.)	
1	69, F	N	520	2.0	0.5	Anterior
2	48, F	N	580	2.8	0.5	Anterior
3	54, M	W	380	1.8	0.3	Anterior
4	65, M	N	780	2.9	0.3	Anterior
5	72, F	W	500	2.0	0.1	Anterior
6	61, M	W	601	1.6	0.7	Apical, posterior, septal
7	66, M	W	610	1.3	0.6	Basal, apical, septal
8	60, M	W	434	1.4	0.4	Anterior, posterior, apical
9	68, F	W	700	2.7	0.3	Diaphragmatic, apical, septal
10	33, M	W	550	2.3	0.4	Posterior, apical
11	72, M	W	630	1.4	0.6	Posterolateral, apical
12	43, M	W	425	1.0	0.6	Anterior, posterobasal, septal
13	67, M	W	393	0.9	0.3	Posterolateral, apical
14	45, M	W	576	1.5	0.6	Posterobasal
15	58, F	N	320	1.7	0.5	Posterior, apical

cardiogram and electrocardiogram of a sixty-eight year old man with a long history of chronic renal disease and arterial hypertension. The QRS s \hat{E} -loop was oriented to the left, superiorly and posteriorly, and rotated in a counterclockwise direction in the frontal plane. The duration of the QRS s \hat{E} -loop was greater than 0.12 second. The loop had a wide ellipsoid configuration, encompassed a large area, and displayed little or no distortion. In this patient the heart weighed 800 gm. and the left ventricle was 3 cm. thick. There was no myocardial infarction. Of the nine patients with left bundle branch block who did not have myocardial infarction at autopsy, six had left ventricular hypertrophy and all but one of these six patients had QRS s \hat{E} -loops of this general configuration. The other patient also had a QRS s \hat{E} -loop which was ellipsoid in configuration, but it was oriented to the left, inferior and anterior to the isopotential point. The spatial vectorcardiogram in left ventricular hypertrophy with left bundle branch block and without left bundle branch block has been described previously in reports from this laboratory [3,5] as well as from others [6,7].

The T s \hat{E} -loop and J in left bundle branch block with left ventricular hypertrophy had the same characteristics as described for uncomplicated left bundle branch block.

Left Bundle Branch Block with Myocardial Infarction. In general, the rotation and direction of the QRS s \hat{E} -loop in left bundle branch block complicated by myocardial infarction is similar to that described for left bundle branch block with left ventricular hypertrophy, the QRS s \hat{E} -loop being inscribed slowly to the left, superiorly and posteriorly. (Fig. 3.) The T s \hat{E} -loop was oriented 180 degrees away, to the right, inferiorly and anteriorly (Fig. 4), and was open, terminating at the junction J which was displaced to the right and anterior to the isopotential point. (Fig. 5.) However, the incidence of QRS s \hat{E} -loops which rotated below the horizontal axis was greater in this series of patients with left bundle branch block and myocardial infarction than in previous studies of patients with left bundle branch block and left ventricular hypertrophy without myocardial infarction [1,3].

Five of the fifteen patients had infarcts of the anterior surface of the heart alone, while the remaining ten had combined lesions. (Table I.) All the patients had left ventricular hypertrophy as well as left bundle branch block and myocardial infarction.

Anterior myocardial infarction: Figure 6 shows the spatial vectorcardiogram of a patient with left bundle branch block and a large infarct of the

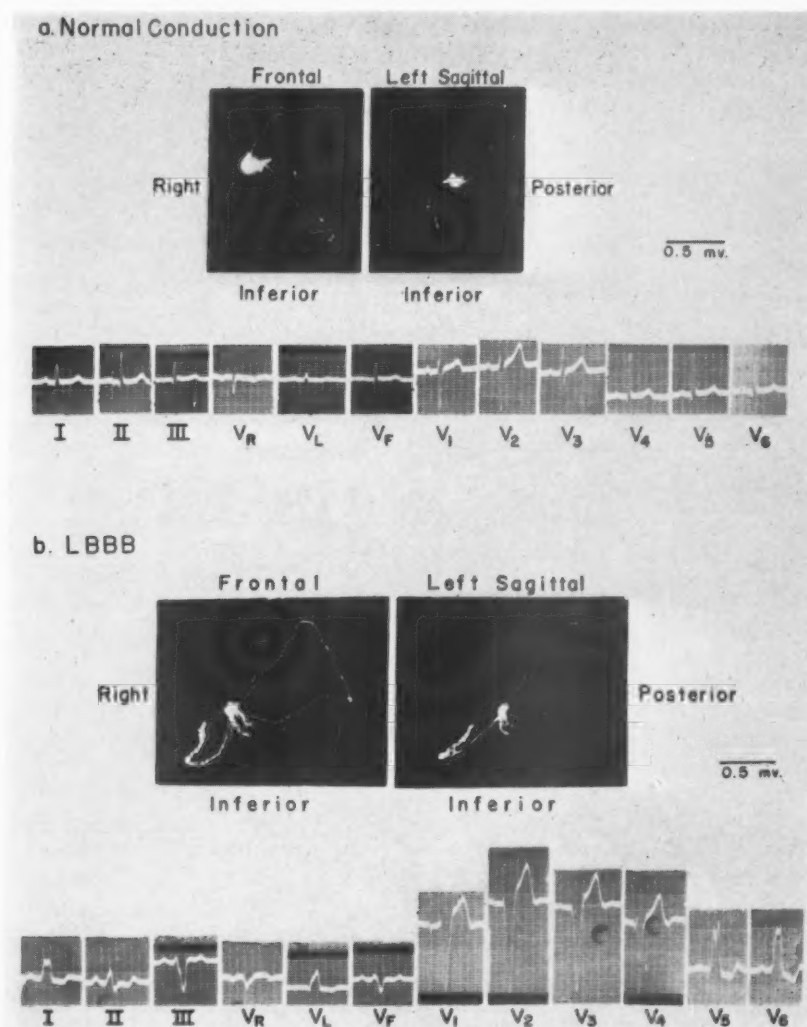


FIG. 1. Spatial vectorcardiogram and electrocardiogram of a fifty-seven year old white woman with transitory left bundle branch block. The figure shows a normal QRS sE-loop and electrocardiogram during normal conduction (A). During left bundle branch block (B), the QRS sE-loop has the configuration often seen in left bundle branch block.

anterior wall of the left ventricle. (Table 1.) The QRS sE-loop of this patient was displaced posteriorly with almost none of the loop anterior to the isopotential point. The initial part of the loop was displaced away from the area of infarction and the QRS sE-loop was distorted. The QRS sE-loops for the other four patients with anterior myocardial infarction displayed the same general configuration.

Combined myocardial infarction: Since the remaining ten patients with left bundle branch block and myocardial infarction had extensive lesions which involved more than one surface of the heart it is not possible to describe a typical spatial vectorcardiographic pattern for this

group. However, one feature, which was common to all and which has not been found on spatial vectorcardiograms of patients without infarction, was the marked distortion of the QRS sE-loop. For example, Figure 7 shows the spatial vectorcardiogram of a patient with extensive anterior, posterior and apical myocardial infarcts. The distortion of the QRS sE-loop is evident. Nevertheless, the general pattern seen in left bundle branch block was retained.

COMMENTS

Wilson and associates [8] considered that it was impossible to diagnose myocardial infarc-

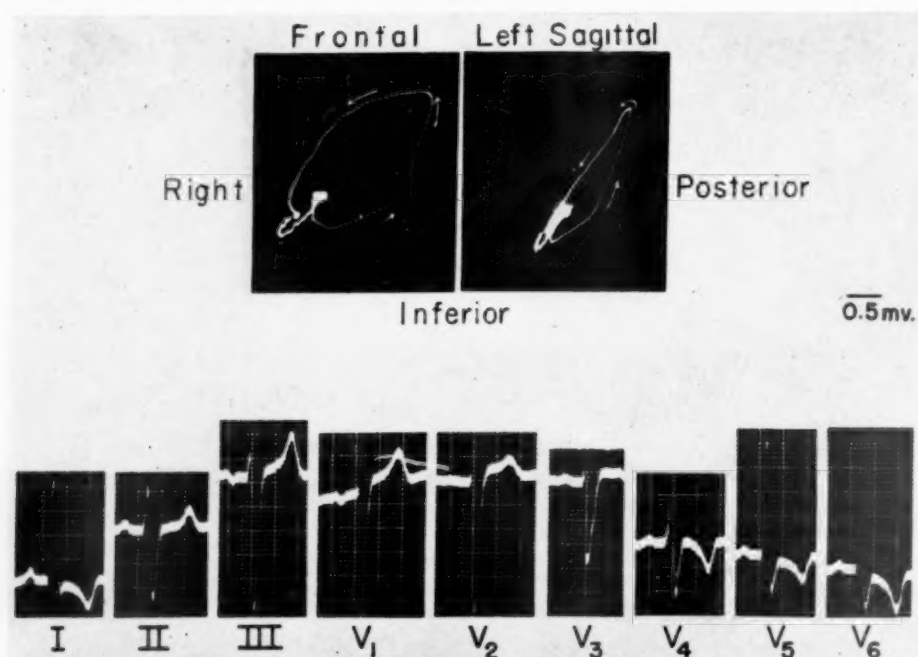


FIG. 2. Spatial vectorcardiogram and electrocardiogram of a sixty-eight year old white man showing the typical configuration of left bundle branch block with left ventricular hypertrophy. Note the smooth, undistorted QRS $s\hat{E}$ -loop and the horseshoe-shaped open T $s\hat{E}$ -loop. No infarct was found at autopsy.

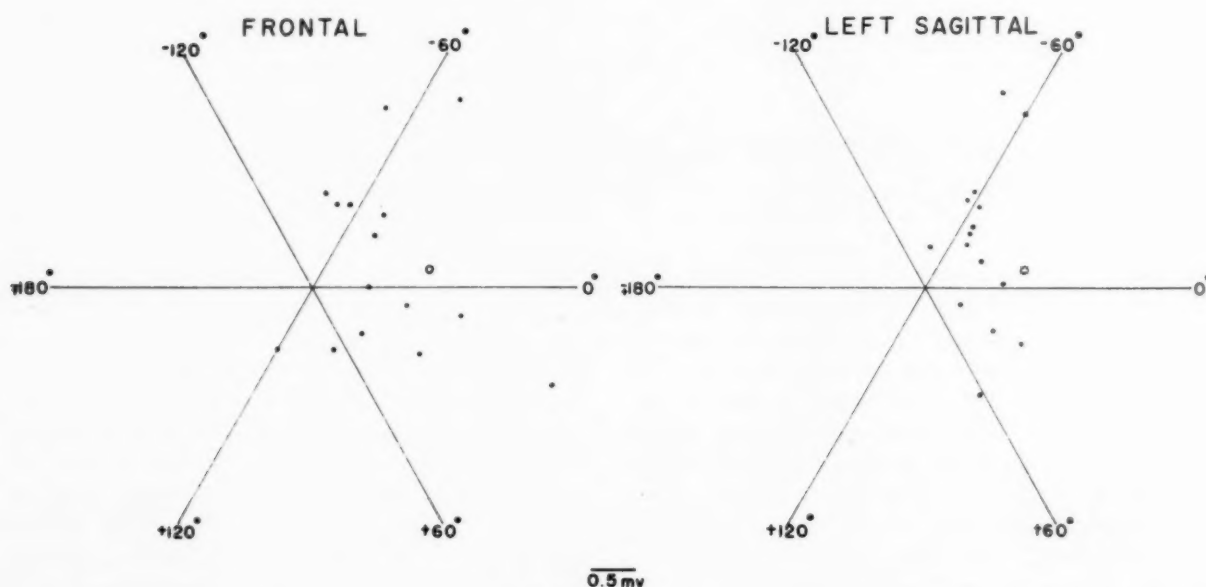


FIG. 3. Magnitude and direction of maximal QRS $s\hat{E}$ vectors in fifteen patients with left bundle branch block and myocardial infarction. The open circle indicates the mean.

tion electrocardiographically in the presence of left bundle branch block. They argued that, when the intraventricular septum is intact, the potential of the left ventricular cavity is initially positive and therefore prevents the formation of Q and QS deflections which are important in

the electrocardiographic diagnosis of infarction. Despite Wilson's reservations, during the twenty years that followed his report many papers were published in which myocardial infarction was considered to be detectable electrocardiographically despite the presence of left bundle

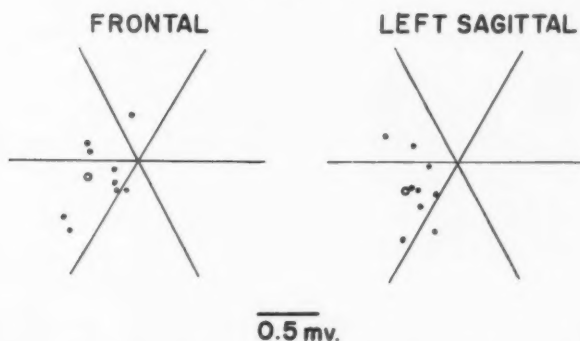


FIG. 4. Magnitude and direction of maximal T vectors in nine patients with left bundle branch block and myocardial infarction in whom this parameter could be measured. The open circle indicates the mean.

branch block [9-12]. Most of these reports dealt with Q waves in lead I and in the precordial leads recorded from the left side of the transition zone, or with the chance finding of intermittent normally conducted complexes which exhibited infarction patterns. However, Chapman and Pearce [13] presented systematic criteria by which myocardial infarction could be recognized from the electrocardiogram in the presence of left bundle branch block. These criteria included Q waves in leads I, aV_1 and V_6 in extensive anteroseptal infarction and rSR' patterns in leads I, aV_1 and V_6 and a notched S wave in the precordial lead to the right of the transition zone in moderately extensive anteroseptal

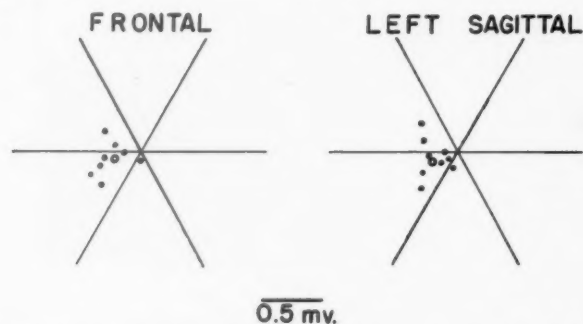


FIG. 5. Spatial position of J in the patients with left bundle branch block and myocardial infarction in whom this parameter could be measured (eight in the frontal plane and nine in the sagittal plane). The open circle indicates the mean.

infarction. Posterior infarction was considered to be present when there was an R' or notching of the R wave in lead aV_1 . Septal infarction was diagnosed by an initial notching of the S wave in lead aV_1 . Of the fifteen patients described in this report, four had myocardial infarction at autopsy which could not be detected from the electrocardiogram using the criteria of Chapman and Pearce. Furthermore, three patients with left bundle branch block and left ventricular hypertrophy in whom no infarction was found at autopsy had electrocardiograms which fulfilled the criteria for myocardial infarction.

Theoretically, at least, it would seem that the time course of depolarization proceeding from

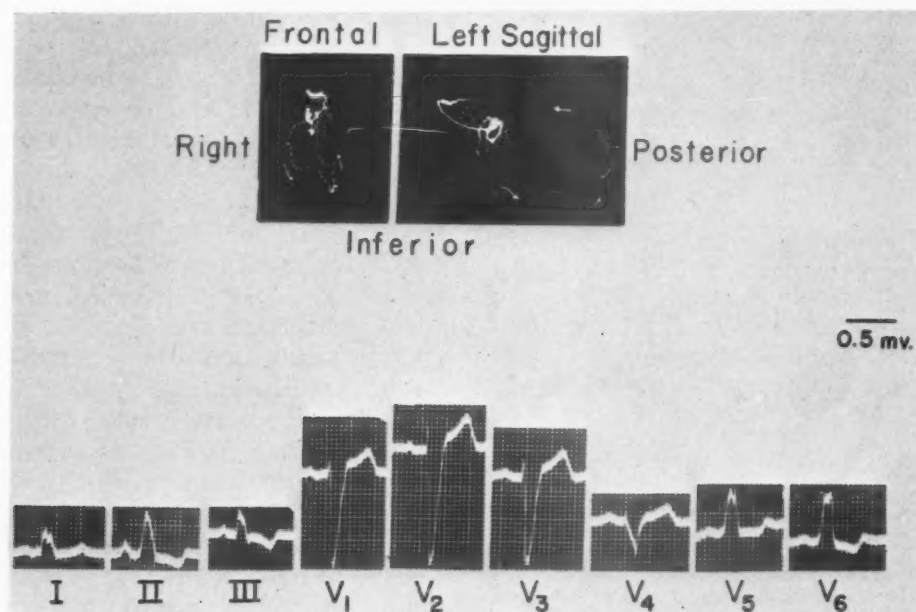


FIG. 6. Spatial vectorcardiogram and electrocardiogram of a patient with an anterior myocardial infarction. The early vectors are oriented away from the area of infarction and the $QRS_{\Sigma}E$ -loop is posterior to the isopotential point. Note the distortion in the loop.

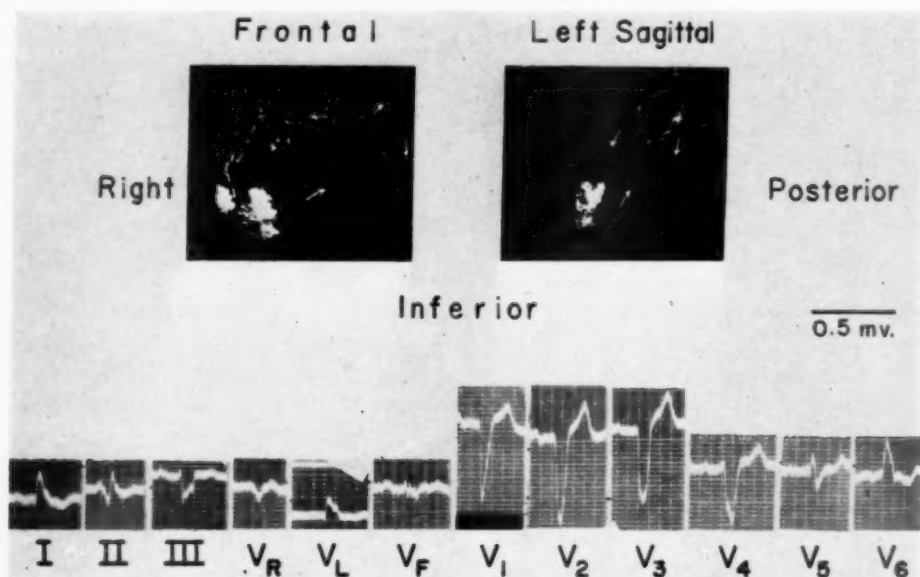
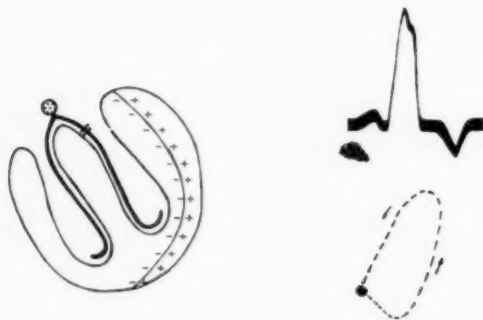


FIG. 7. Spatial vectorcardiogram and electrocardiogram of a patient with myocardial infarctions involving more than one surface of the heart. Note the marked distortion in the QRS $s\hat{E}$ -loop. See text for details.

the right side of the septum because of the presence of left bundle branch block and progressing

a. Without Infarction



b. With Infarction

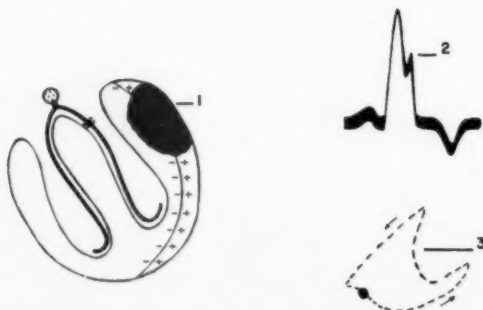


FIG. 8. Schematic representation of theoretic QRS $s\hat{E}$ -loops and electrocardiogram in left bundle branch block with a normal myocardium and in left bundle branch block with myocardial infarction. See text for details.

through an essentially normal left ventricle would differ from the time course of a process of depolarization which progresses through a left ventricle in which large masses of muscle are rendered electrically inactive as a result of infarction. Therefore, were it possible to compare in detail the time courses of depolarization in patients with a normal myocardium and a localized lesion of the left bundle branch with the time courses of depolarization in those with left bundle branch block and myocardial disease, differences in these time courses should be recognizable despite the presence of left bundle branch block. (Fig. 8.) Fortunately, the spatial vectorcardiogram displays the time course of depolarization in fairly good detail. Figure 8 shows a schematic representation of this concept. The loss of muscle and, in turn, electrical forces might be expected to produce distortions in the QRS $s\hat{E}$ -loop such as were described and which can be seen in Figure 7.

While the spatial vectorcardiogram in left bundle branch block has been previously described [3,6,14], reports of left bundle branch block complicated by myocardial infarction are rare. Deglaude and Laurens [15] described two cases, confirmed at autopsy, in which they considered the vectorcardiogram to be diagnostic of myocardial infarction. They based their opinions primarily on the distortions found in the QRS $s\hat{E}$ -loop. Wenger and Hupka [16]

considered an initial anterior displacement of the QRS sÊ-loop followed by an abrupt posterior displacement to be the most important change in the spatial vectorcardiogram in posterior myocardial infarction.

SUMMARY

The spatial vectorcardiograms of fifteen patients with left bundle branch block complicated by myocardial infarction located at autopsy are presented. Distortions in the QRS sÊ-loops not usually found in patients with left bundle branch block without myocardial infarction are described. A theoretic basis for the distortions in the QRS sÊ-loop due to myocardial infarction was suggested. Continued correlation of the spatial vectorcardiogram in left bundle branch block with autopsy studies should increase the usefulness of this type of tracing in the resolution of an extremely difficult problem; namely, the detection of myocardial infarction in the presence of left bundle branch block.

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Hemodynamics During Induced Cardiac Tamponade in Man*

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A SMALL decrease in arterial pulse amplitude (in systolic, diastolic and pulse pressures) occurs on inspiration in normal persons. Kussmaul [7] in 1873 applied the term "pulsus paradoxus" to the accentuation of this phenomenon which he observed in patients with pericardial disease. After calling attention to the exaggerated respiratory variation in the amplitude of the peripheral arterial pulse, he pointed out that, *paradoxically*, no such respiratory variation could be palpated over the precordium. Clearly, the "paradox" involved a uniform and unchanging precordial impulse in the face of a peripheral pulse which waxed and waned with respiration. This information notwithstanding, several who have written about pericardial disease [2,3,10] have pointed out that the paradoxical pulse is really not paradoxical in the sense of a reversal of the normal phase or time relationship between respiration and the pulse. § A tacit implication of such a statement is that Kussmaul was somehow mistaken about the phase relationship between respiration and pulse amplitude. As already pointed out, however, it seems clear that Kussmaul never had this sort of paradox at all in mind. While it is thus possible to exonerate Kussmaul of error in clinical observation, his judgment in choosing the term "pulsus paradoxus" can hardly be commended, since there can be little argument that it invites misinterpretation. Although any alternative phrase is apt to be unwieldy, it would seem

§ Parenthetically, the venous pulse phenomenon bearing the name of Kussmaul's sign is "paradoxical" in the sense that the usual phase relationship between respiration and venous pressure is reversed: the venous pressure rises instead of falling on inspiration.

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to be desirable to use a phrase connoting something of the exaggerated respiratory variation in pulse amplitude characteristic of the condition. We shall henceforth in this paper use the term "exaggerated respiratory pulse variation," for reasons which constitute the principal subject of this communication.

Since the experiments of Cohnheim [4] in 1889 various observations on experimental animals and man have clarified the dynamics of cardiac constriction and pericardial tamponade. In 1954 Isaacs, Berglund and Sarnoff [5], studying experimental tamponade in the dog, pointed out the importance of a lowered "effective ventricular filling gradient" in producing the diminished cardiac output which is characteristic of cardiac tamponade. Much earlier (1924) Katz and Gauchat [6] had explained, in a series of brilliant animal experiments strategically bolstered by careful clinical observations, the exaggerated respiratory pulse variation showing how the effective left ventricular filling gradient was decreased during inspiration in tamponade. They showed that the tense pericardial sac with its fluid contents blocked to a great extent the transmission of intrathoracic pressure to the space surrounding the heart (pericardial space). By contrast, the inspiratory decrease in intrathoracic pressure was well transmitted to the pulmonary capillaries and veins from which the left ventricle fills. Consequently, in response to the negative inspiratory intrathoracic pressure, the pulmonary venous pressure reflected comparable swings of negative pressure, whereas the pressure surrounding the ventricles (intra-pericardial pressure) varied little with respiration. Therefore the difference between the

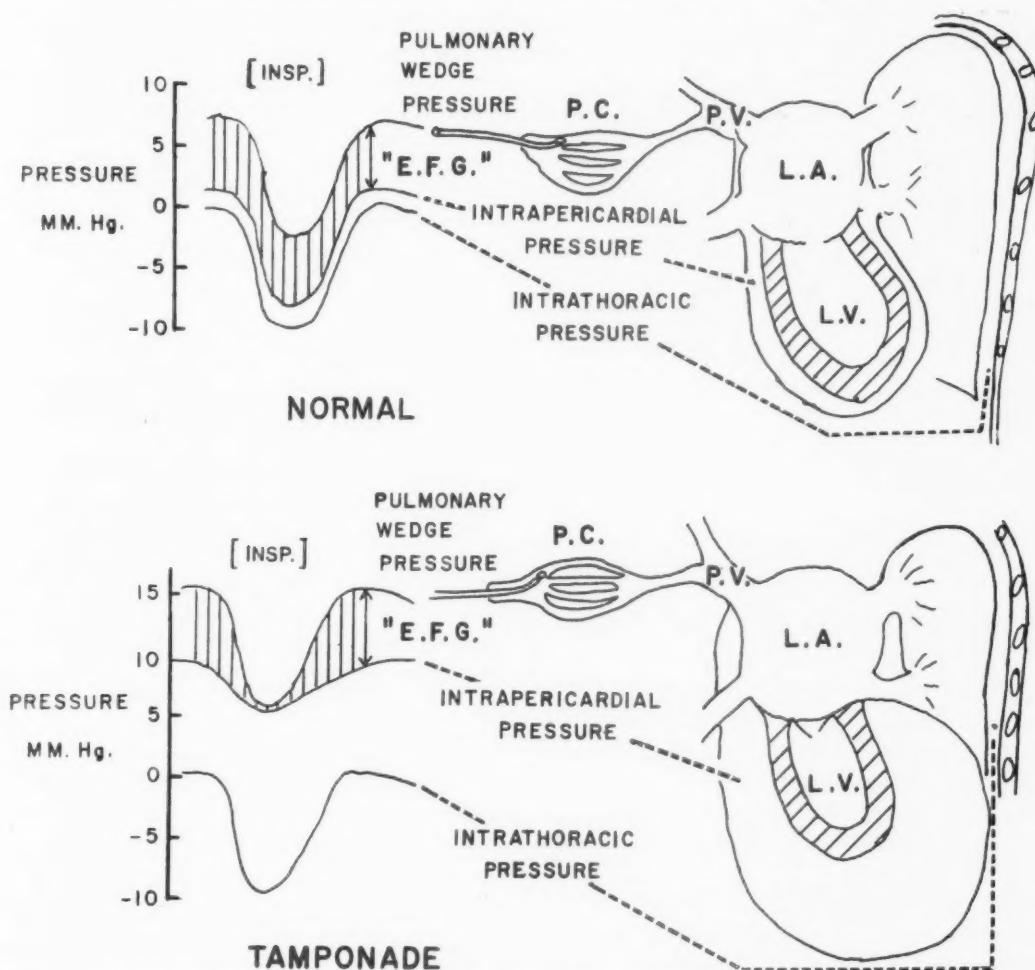


FIG. 1. The top half of the figure represents the normal status in which changes in intrathoracic (pleural) pressure are faithfully transmitted to both the pericardial sac and the pulmonary veins and capillaries; thus the effective filling gradient (E.F.G.) of the left ventricle changes only slightly through the respiratory cycle. The bottom half of the figure represents the situation in tamponade, in which changes in intrathoracic pressure are transmitted well to the pulmonary veins and capillaries but are transmitted poorly to the thickened and distended pericardial sac. Here the effective filling gradient (E.F.G.) of the left ventricle becomes much less during inspiration than during expiration.

pulmonary venous pressure and the intrapericardial pressure was less during inspiration than during expiration; this difference between the pressure surrounding the left ventricle and the pressure in its filling reservoir represented the "effective filling gradient" of the left ventricle (or more accurately, if the possibility of diastolic suction is ignored, the upper limit of this gradient). The response of the left ventricle to the inspiratory decrease in filling gradient was the diminished inspiratory stroke volume characteristic of pulsus paradoxus. This mechanism is shown schematically in Figure 1.

To our knowledge the critical observations necessary to establish that this mechanism also operates in human subjects with pericardial

disease have not yet been made. It is the purpose of this communication to present such observations. They were made on a patient with bronchogenic carcinoma with pericardial invasion. Rapid reaccumulation of pericardial fluid necessitated frequent needle punctures of the pericardial sac which were finally circumvented by the introduction of an indwelling polyethylene tube into the pericardial sac. It was found that this tube was sealed to the pericardial sac well enough to allow pressure in the pericardial sac to be measured accurately. When a small volume of fluid was added to the pericardial space the pericardial pressure rose and fell back toward normal quite slowly (1 to 2 mm. Hg in ten minutes). This suggested that acute

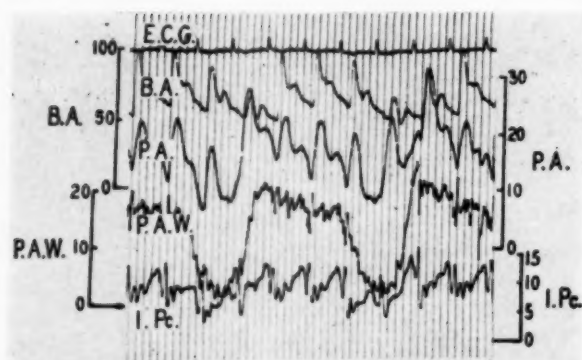


FIG. 2. An oscillographic tracing taken during tamponade of (from top to bottom) lead II of the electrocardiogram (E.C.G.), brachial artery pressure (B.A.), pulmonary artery pressure (P.A.), pulmonary artery wedge pressure (P.A.W.), and intrapericardial pressure (I.Pc.). Note the prominent respiratory variations in the B.A., P.A. and P.A.W. pressure tracings and the virtual absence of respiratory effects upon the intrapericardial pressure.

and reversible tamponade experiments could be carried out. The clinical, physiologic and necropsy data in this case suggest that the abnormalities present combined the effects of pericardial constriction by tissue (in this instance malignant tissue) and of tamponade produced by filling the rather limited pericardial space with fluid.

METHODS AND EXPERIMENTAL PROCEDURE

Cardiac catheterization was conducted in the usual manner. Intravascular pressures were measured by strain gauge transducers and recorded on a photographic oscillograph. The cardiac output was determined by the Fick principle, with sampling of mixed venous blood from the pulmonary artery and of arterial blood from the brachial artery. Expired gas, measured in a Tissot spirometer, was analyzed for oxygen and carbon dioxide in a Scholander micro-analyzer. Blood samples were analyzed by the method of Van Slyke and Neill. All pressure transducers were calibrated by mercury manometers at the beginning and end of the procedure.

Following premedication with Nembutal® and Demerol® the patient was brought to the catheterization laboratory in the fasting state. A double-lumen Courmand catheter was introduced, its tip being placed in the right ventricle and its proximal lumen in the right atrium; these pressures together with the pericardial pressure were recorded. After repetition to assure that these pressures were stable and reproducible, the catheter was advanced to the pulmonary "wedge position," the pulmonary wedge pressure being recorded through the distal lumen and the pulmonary artery pressure through the proximal lumen. A Riley needle was inserted into the left brachial artery, and the brachial artery pressure, pulmo-

nary artery pressure, pulmonary wedge pressure and intrapericardial pressure were recorded simultaneously with lead II of the electrocardiogram. (Fig. 2.) After measuring the patient's minute ventilation and ascertaining that it as well as the heart rate and vascular pressures were stable, the cardiac output was measured. Twenty minutes later the vascular pressures were recorded again and found to be unchanged from those previously recorded. This twenty-minute interval served as the control period. The control cardiac output was not repeated. Shortly after these observations, at intervals of two or three minutes (Fig. 3), 50 ml. increments of warmed saline solution were injected into the pericardial sac, before and after which vascular pressures and intrapericardial pressures were measured.

In twenty-one minutes 250 cc. of saline solution were injected into the pericardial sac. At this point, because of the patient's pallor, tachycardia and venous distention, no further filling of the pericardial sac was attempted. The cardiac output was redetermined at this time and the intracardiac pressures recorded again, together with intrapericardial pressures. The saline solution was allowed to remain in the pericardial sac for a period of twenty-four minutes during which time repeated observations of vascular pressures and pericardial pressure were made. At the end of this period, however, the patient began to complain of dyspnea, and rales appeared over both basal lung fields. The catheter was therefore withdrawn to the right ventricle and atrium, and after these pressures were recorded simultaneously with pericardial pressure, as much fluid as could be obtained (150 cc.) was aspirated from the pericardial sac. After thirty minutes, during which the patient experienced relief from his dyspnea, the vascular pressures were again recorded and the cardiac output estimated once more. Unfortunately the expired gas collection from the last cardiac output was lost, and only the arteriovenous oxygen difference is available. This terminated the experiment.

RESULTS

The results of the experiment are summarized in Figure 3.

The Cardiac Output. With injection of 250 ml. of saline solution into the pericardial sac the cardiac output fell from 7.7 to 5.7 L./minute. The decrease in the cardiac index was from 4.9 to 3.6 L./minute/M². Inasmuch as the heart rate increased from 109 to 126 beats per minute in the interval between the estimations of cardiac output, the stroke volume fell to a greater extent than did the cardiac output, decreasing from 71 to 45 ml. The expired gas collection from an intended third cardiac output measurement following removal of the pericardial fluid was lost but it could be ascertained that the arteriovenous

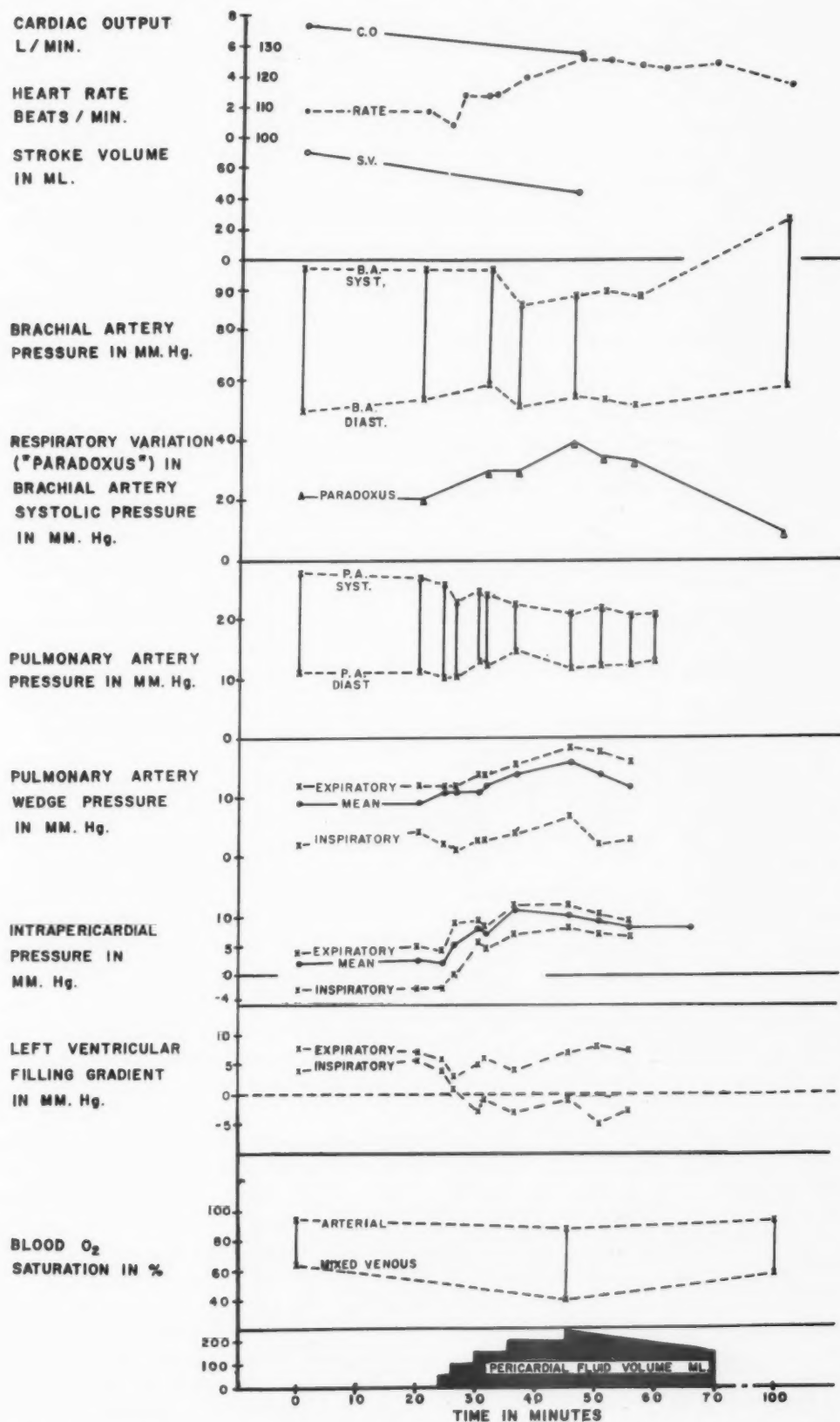


FIG. 3. A graphic summary of the hemodynamic alterations during induced tamponade. See text for discussion.

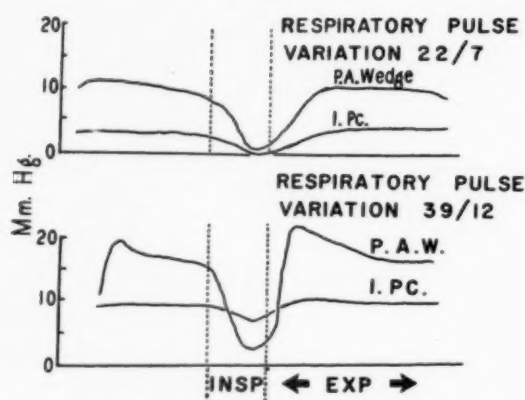


FIG. 4. Redrawn tracings of pulmonary artery wedge (P.A.W.) and intrapericardial (I.Pc.) pressures before (above) and during (below) induced tamponade. The difference between these two curves represents the effective filling gradient of the left ventricle during diastole. During tamponade the difference between inspiratory and expiratory gradients is markedly increased, the gradient appearing to be negative during the latter portion of inspiration in tamponade. Superimposed higher frequency variations due to cardiac activity have been smoothed out in redrawing. Baseline zeros and sensitivity are the same for both pressures.

difference decreased from the tamponade value toward the previous control level; this suggests that the cardiac output rose again following removal of the pericardial fluid. The cardiac indices, both before and during cardiac tamponade, are above the usual resting level for this laboratory. However, the disseminated tumor may have increased the basal metabolic rate, a phenomenon known to occur in some patients with disseminated malignancy. Alternatively, pain and apprehension may have rendered the patient "non-basal." At any rate the oxygen consumption per square meter of body surface was increased during both cardiac output determinations (183 and 212 ml./minute/M²).

Systemic Arterial Pressure; Respiratory Variation in Pulse Amplitude. With the injection of fluid into the pericardial sac and the accompanying rise in intrapericardial pressure the systemic arterial mean pressure fell somewhat, and the pulse pressure fell to a slightly greater extent. The respiratory variation in systolic pressure was further exaggerated, increasing from 22 mm. Hg in the control observations to 39 mm. Hg at the height of cardiac tamponade. Prompt reversal of these changes occurred on withdrawal of the pericardial fluid.

Pulmonary Artery and Pulmonary Wedge Pressures. In the pulmonary artery there was little change in the mean pressure and a moderate decrease in

the pulse pressure. At the same time the respiratory variations in systolic and diastolic pressures of the pulmonary artery were somewhat greater during tamponade than during the control period, and approximately the same as the respiratory variations observed in the "pulmonary artery wedge" pressure. For this reason the respiratory variations are presented in Figure 3 only in the pulmonary wedge pressure and not in the pulmonary artery pressure. The pulmonary wedge mean pressure rose from 9 to 16 mm. Hg; accompanying this rise was an increase in the respiratory fluctuations in this pressure which in the control period amounted to 9 mm. Hg and with tamponade rose to 15 mm. Hg. This was due almost entirely to a rise in the wedge pressure during expiration. (Fig. 4.)

Intrapericardial Pressure. It can be seen that the intrapericardial pressure rose by approximately 3 mm. Hg for every 50 ml. of saline solution injected into the pericardial sac. The respiratory variation in the pericardial sac narrowed progressively with increasing pericardial pressure whereas respiratory pressure variations present in the pulmonary artery wedge (and presumably in the intrapleural space) widened progressively with the institution of tamponade.

Left Ventricular Effective Filling Gradients. The "effective filling gradient" of the left ventricle during inspiration and expiration is shown graphically in Figure 3. This gradient was calculated by subtracting the pericardial pressure from the pulmonary wedge pressure during mid-expiration and during mid-inspiration. This value, as indicated earlier, is nearly the same as the diastolic gradient between the pulmonary veins and the ventricular cavity and must represent the upper limit of this gradient, barring significant ventricular diastolic suction. During the "control" observations this gradient averaged plus 4 mm. Hg during inspiration and plus 8 mm. Hg during expiration. During tamponade, the inspiratory gradient varied between minus 1 and minus 5 mm. Hg and the expiratory gradient was plus 7 to plus 8 mm. Hg. Coincident with this widening of the difference between the inspiratory and expiratory gradients the inspiratory decrease in brachial artery systolic pressure changed from 22 to 39 mm. Hg.

Right Atrial and Right Ventricular Pressures. The intrapericardial pressure was consistently below the atrial pressure and the ventricular diastolic pressure both in the control and the

tamponade state. The ventricular pressure curve in both states, although not showing the typical dip and plateau pattern described in constrictive pericarditis [7] and in tamponade [8], did suggest a protodiastolic dip with rapid rise in pressure in mid-diastole and a near-plateau late in diastole.

COMMENTS

Both before and after adding fluid to the pericardial sac there was a marked discrepancy between respiratory fluctuations in the pulmonary wedge pressure on the one hand and the pericardial sac on the other hand. This is shown diagrammatically in Figure 4 in which pulmonary wedge pressure and intrapericardial pressures only have been redrawn with the same baseline zero and with the same sensitivity in the control and tamponade states. There was clearly an exaggerated respiratory variation in the brachial artery pressure even in the control period, which is believed to be related to the thickening of the pericardial sac which damped and attenuated the intrathoracic pressure during its transmission to the pericardial contents. Increasing intrapericardial pressure by adding saline solution to the pericardial sac had the effect of raising the diastolic pressure levels in both atria and ventricles, decreasing the mean left ventricular filling gradient to some extent, and decreasing the inspiratory filling gradient even more. This resulted in a lowered cardiac output with diminution particularly of the stroke volume during inspiration, the period during which the effective left ventricular filling gradient was lowest and indeed appeared to be negative (retrograde flow would be prevented by the mitral valve). The observations presented appear to be similar to the phenomenon recently reported by Murphy, Meyer and Chase [9] who described two patients with constrictive pericarditis and reversible congestive phenomena. Evidence was presented by them to indicate that fluid accumulation in and reabsorption from a rigid pericardial space was the responsible mechanism.

It has been stated [10] that pulsus paradoxus occurs in the pulmonary artery as well as in the systemic arterial system. Although respiratory fluctuations were indeed seen in the pulmonary artery pressure in our case, it is probable that these represented direct transmission of intrathoracic pressure to the vasculature of the lung and not variations in the stroke volume of the

right ventricle. In support of this interpretation, we observed in the present case during tamponade that right atrial pressure varied little on inspiration and that these variations were *less* than those seen in the pericardial sac. The jugular venous pressure did not fluctuate appreciably with respiration. Thus there was no evidence that the effective filling gradient of the right ventricle varied with respiration, as was true of the effective filling gradient for the left ventricle. At least in this case the mechanisms for inspiratory decrease in the pulmonary and systemic arterial pressures appear to be different.

However, respiratory variations in the pulmonary wedge pressure were of greater amplitude during tamponade than in the control state. (Fig. 5.) This was true also of respiratory variations in the pulmonary artery pressure. These probably reflect an increased amplitude of intrathoracic pressure variation because of an increase in tidal volume (from 535 to 690 ml.) and altered pulmonary mechanics. Pulmonary compliance is known to decrease and pulmonary resistance to increase when the "pulmonary capillary" pressure is increased, as in this study [11,12]. In addition, the occurrence of dyspnea and pulmonary rales during tamponade strongly suggested an increase in pulmonary congestion.

Katz and Gauchat [6], on the other hand, were able to demonstrate that variations in filling gradient occurred with respect to the right ventricle as well as the left ventricle, although these variations were small, of the order of 2 mm. of saline solution.

CONCLUSIONS

A study of the hemodynamic effects of pericardial tamponade is described in a patient in whom the epicardium and pericardium were involved by bronchiogenic carcinoma. The necessity for frequent pericardial aspiration led to permanent cannulation of the pericardial sac, thus providing an opportunity to perform an acute tamponade experiment in man.

Data are presented which indicate that a diminished "effective left ventricular filling gradient" during inspiration is responsible for the decreased inspiratory stroke volume and the exaggerated respiratory pulse variation characteristic of tamponade. Thus the mechanism for the exaggerated respiratory pulse variation suggested by Katz and Gauchat on the basis of animal experiments appears to apply in man.

Although respiratory variations in the pul-

monary artery pressure were greater during tamponade than in the control period, the data indicate that the mechanism responsible for this is not an inspiratory decrease in the effective filling gradient of the right ventricle but simply transmission to the lung vasculature of greater pleural pressure swings. The probable reasons for greater amplitude of pleural pressure variations in tamponade are hyperventilation and altered pulmonary mechanics due to pulmonary engorgement.

It is suggested that the euphonious but misleading term "pulsus paradoxus" be abandoned in favor of the phrase "exaggerated respiratory pulse variation."

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Asterixis in Non-Hepatic Disorders*

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ASTERIXIS, which is generally known as the "liver flap" or flapping tremor, was first described by Adams and Foley in 1949 as a characteristic neurologic abnormality of impending hepatic coma [1]. This sign is usually elicited by having the patient extend the forearms horizontally and dorsiflex the wrists. The appearance of sudden, rapid, arrhythmic flexion-extension flapping movements at the wrists gives this phenomenon its colloquial name. Similar to and fro movements may occur on sustained positioning of the elbows, tongue, eyelids or fingers. Further observations suggested that these movements represent momentary lapses in the ability to maintain a posture, followed almost immediately by resumption of the original position. Electromyography has demonstrated a brief hiatus in the electrical activity of the contracted muscles which appears to coincide with the flapping motion. Adams and Foley coined the term asterixis (from the Greek *sterigma*) which literally means the inability to maintain a fixed posture [2]. This neurologic sign has come to be recognized as the trademark of impending hepatic coma.

The syndrome of impending hepatic coma, which consists of impaired consciousness, asterixis, hyperammonemia and frequently fetor hepaticus, occurs in patients with severe hepatic parenchymal disease or can be precipitated in cirrhotic patients by the ingestion of ammonium salts, urea, a high protein diet [3], or the absorption of blood from the gastrointestinal tract [4]. In addition, a variety of chemical compounds including acetazoleamide [5], chlorothiazide [6-8], methionine [9] and amphenone [10-12] may induce impending hepatic coma or a picture indistinguishable from it in patients with liver disease. Furthermore, a variety of non-specific factors such as infection, surgical trauma, paracentesis, abnormalities of serum electrolytes, and the administration of narcotic, sedative or tranquilizing drugs may bring about "impending

ing hepatic coma" in cirrhotic patients [4,11,13].

Asterixis has also been observed in cerebral insufficiency of non-hepatic origin. Adams and Foley in their early descriptions reported it in patients with uremia, hypokalemia and polycythemia with heart failure [2,14]. During the past decade asterixis has been observed in patients with mental confusion or stupor in a variety of non-hepatic disorders. Most common among them is chronic pulmonary insufficiency with carbon dioxide narcosis [15-17]. It has been observed also in idiopathic steatorrhea, Whipple's disease and other malabsorptive syndromes [4,18]. In one such patient it appeared to be related to the presence of magnesium deficiency [18]. It has also been described in uremia [14,19,20], bromide intoxication [21] and following the intravenous administration of ammonium chloride [11,22].

The mechanism responsible for asterixis is unknown. The diversity of metabolic disturbances in which it is encountered argues against a single etiologic factor. The similarity of the electroencephalographic patterns in these different diseases, including hepatic coma [20,23,24], uremia [20,25], chronic pulmonary insufficiency [16,25] and other disorders [20,26,27], implies that this electroencephalographic pattern may arise from many causes. Perhaps many metabolic or toxic disturbances, each acting in a characteristic manner, may depress cerebral metabolism and thus induce a non-specific syndrome of impaired consciousness, asterixis and electroencephalographic slowing [17]. The observation that decreased cerebral oxygen uptake occurs in hepatic coma [28,29], uremia [30-32] and other disorders [32-34] suggested that decreased cerebral oxygen utilization might be the factor common to all these diseases.

The present study was undertaken to correlate asterixis with the clinical, biochemical and electroencephalographic findings in patients with both hepatic and non-hepatic disorders.

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TABLE I
DIAGNOSIS AND PRECIPITATING FACTORS

Case No.	Severity of Delirium*	Primary Diagnosis	Precipitating Factors
1	1	Pulmonary emphysema and fibrosis	CO ₂ narcosis; respiratory infection
2	1	Pulmonary emphysema and fibrosis	Pneumonia; CO ₂ narcosis
3	2	Pulmonary emphysema and fibrosis	Respiratory infection; O ₂ ; CO ₂ narcosis
4	2	Pulmonary emphysema and fibrosis	CO ₂ narcosis; ?acetazoleamide
5	1	Pulmonary emphysema and fibrosis	CO ₂ narcosis; ?acetazoleamide; ?chlorothiazide
6	2	Bronchogenic carcinoma	Bronchial aspiration
7	2	Bronchogenic carcinoma	Pneumonia
8	2	Cardiovascular arteriosclerosis	Congestive heart failure
9	2	Cardiovascular arteriosclerosis	Cheyne-Stokes respiration
10	1	Bronchiectasis	Septicemia, acute glomerulitis
11	3	None	Glutethimide intoxication
12	1	Chronic lymphocytic leukemia	Septicemia
13	1	Laennec's cirrhosis	Rectal hemorrhage; hepatic necrosis
14	2	Hemochromatosis	High protein diet
15	2	Laennec's cirrhosis	Chloral hydrate
16	2	Metastatic cholangioma	Hepatic metastases and infarction
17	2	Metastatic seminoma	Prochlorperazine toxicity

* Graded 1 to 4.

MATERIALS AND METHODS

All patients were admitted to the West Haven Veterans Administration Hospital or the Grace-New Haven Community Hospital between February and October 1958. The diagnoses were established in these patients by the usual clinical, chemical and histologic criteria. (Table I.)

All seventeen patients were men who ranged in age from twenty-three to eighty-three years, with a mean age of fifty-eight. The twelve patients with non-hepatic disorders averaged sixty-two years. The primary diagnosis, precipitating cause and severity of the state preceding hepatic coma are presented in Table I. Five patients (Cases 1 to 5) had pulmonary emphysema and fibrosis with ventilatory insufficiency. Two (Cases 6 and 7) had advanced bronchogenic carcinoma with partial obstruction of the airway. Two (Cases 8 and 9) had severe generalized arteriosclerosis with congestive heart failure which was responsible for their chronic organic psychosis. Three patients with cirrhosis were studied, one (Case 13) with severe hepatic necrosis, one (Case 14) with protein intoxication, and the third (Case 15) with chloral hydrate overdosage. The other five patients had miscellaneous diseases which included uremia (Case 10), glutethimide (Doriden®) overdosage (Case 11), prochlorperazine (Compazine®) intoxication (Case 17) and septicemia in a patient with lymphocytic leukemia (Case 12). In general these patients were seriously ill and more than two thirds of them have since died. These cases were complicated, and it is an oversimplification to attribute the flapping tremor to one facet of the disease, for example, to prochlorperazine in a patient who also had a metastatic malignancy (Case 17).

Brief case histories are appended to allow more complete analysis of these cases.

The arterial hydrogen ion concentration was determined with a Cambridge Model R pH meter. Arterial oxygen saturation was measured by either the Van Slyke and Neill manometric technic [35] or the Wood ear oximeter [36], and the data are so designated. Liver function tests and serum protein determinations were made according to methods reported from these laboratories [37]. Blood ammonia was estimated by the technic of Seligson and Hirahara [38]. Blood urea nitrogen, blood sugar and serum carbon dioxide, sodium, chloride and potassium were performed by standard laboratory technics. Serum magnesium was estimated by a modification of the method of Orange and Rhein [39].

Electroencephalograms were recorded with the Grass Model 3D 8-channel apparatus. Abnormal electroencephalograms were arbitrarily classified into five grades (Fig. 1): *grade 0*: normal; *grade I*: unstable alpha rhythm with some random 4 to 6 c.p.s. waves; underlying fast activity was sometimes present; *grade II*: some alpha rhythm persisted but runs of medium voltage 4 to 6 c.p.s. activity were present; occasional 2 to 4 c.p.s. activity; *grade III*: almost continuous 4 to 6 c.p.s. activity; *grade IV*: almost entirely high voltage 2 to 3 c.p.s. activity.

Studies were performed when asterixis was present. The patients displayed varying degrees of confusion or disorientation, but all were able to assume the asterixis test position. The mental status was graded as follows: *grade 0*: normal; *grade 1*: vague change in personality; euphoria, apathy or minimal confusion; *grade 2*: confusion, disorientation; *grade 3*: semi-stuporous but responsive; *grade 4*: comatose.

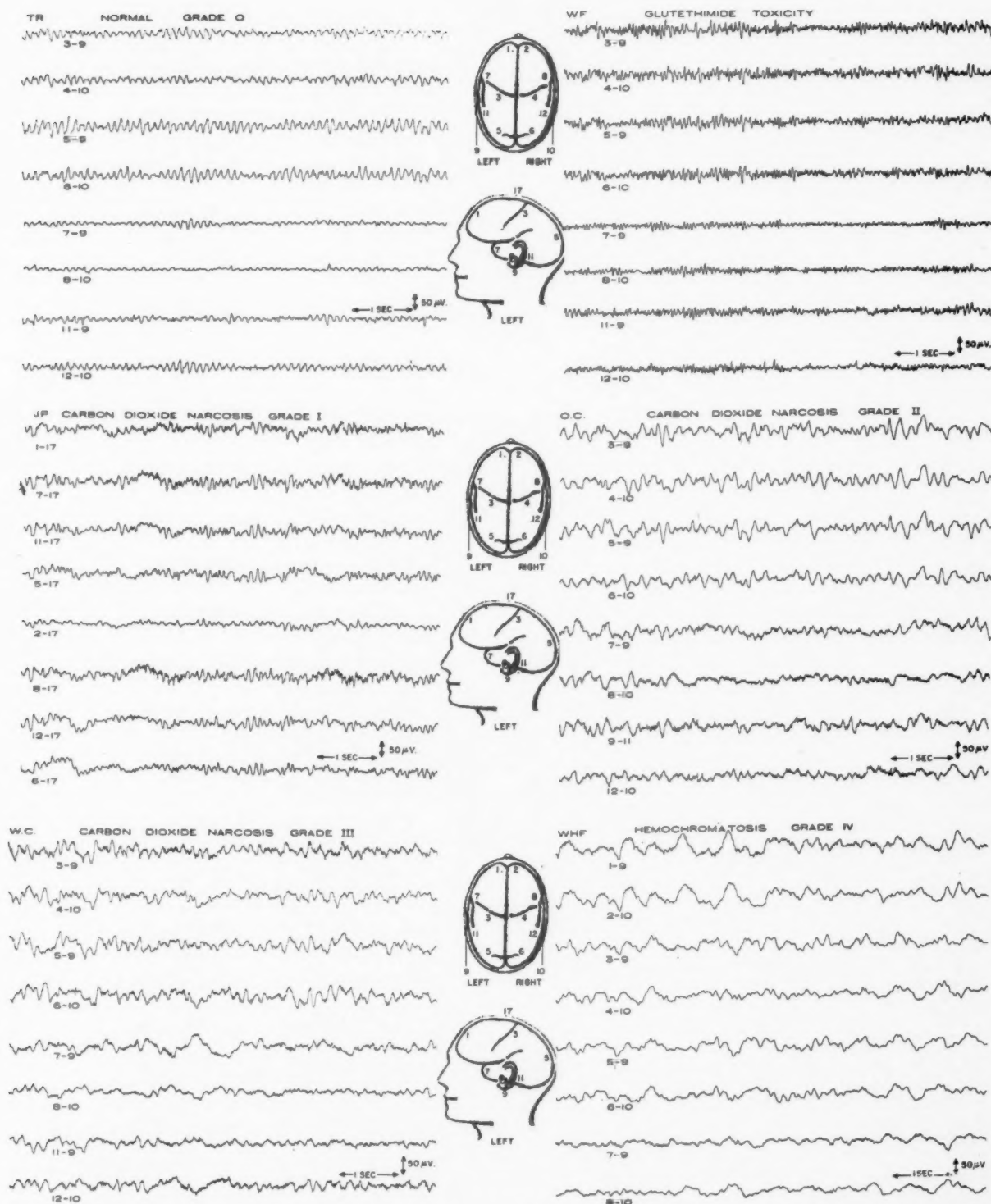


FIG. 1. A normal electroencephalographic pattern is shown in the upper left. The other electroencephalographic tracings were recorded from patients with asterixis. In the upper right is depicted the almost continuous fast activity observed in the patient with glutethimide intoxication. Progressively more abnormal patients (Grade I through Grade IV), characterized by high voltage slow waves, are shown in the middle and lower portions of the figure. The numbers indicate electrode positions.

TABLE II
BLOOD CHEMISTRY DETERMINATIONS

Case No.	Blood Urea Nitrogen (mg./100 ml.)	Blood Sugar (mg./100 ml.)	Serum Electrolytes (mEq./L.)					
			Carbon Dioxide	Chloride	Sodium	Potassium	Magnesium	Calcium
1	19	94	34	90	136	5.0	2.2	4.8
2	27	67	40	86	143	5.0	2.2	...
3	36	93	144	...	2.2	4.8
4	32	123	27	96	136	5.9	1.9	5.0
5	26	70	35	90	138	4.5	2.0	4.6
6	24	127	30	87	137	5.5	1.8	4.6
7	11	123	33	96	144	5.2	2.0	5.1
8	34	80	23	108	139	4.0	1.7	...
9	29	109	26	106	142	5.1	2.2	...
10	172	...	12	103	140	5.9	2.7	4.4
11	24	102	139	4.0	2.0	...
12	22	102	26	90	127	5.4	1.9	4.6
13	13	106	20	90	122	3.3	1.9	4.4
14	13	...	26	106	137	4.4	1.6	5.2
15	5	...	27	92	128	3.8	1.5	...
16	18	68	25	...	134	5.1	2.0	5.9
17	7	1.9	...

A variety of neurologic abnormalities accompanied asterixis in these patients. In one (Case 3) a unilateral extensor plantar reflex, which was noted at the time asterixis was first detected, persisted until the flap disappeared. Ataxia and dysidiadokokinesia were present in patients with glutethimide toxicity (Case 12) and in ammonia intoxication (Case 14). In the latter patient Parkinsonian-like rigidity and a "pill rolling" tremor at rest were also noted. Varying degrees of muscle rigidity occurred in four other patients (Cases 3, 9, 13 and 17). Transient dilatation of one pupil accompanied asterixis in one patient (Case 10). Muscle fasciculations were observed in three patients (Cases 6, 9 and 10), usually preterminally. No remarkable abnormalities of the central nervous system were observed at postmortem examination of those patients so studied.

RESULTS

Blood Chemistry Determinations (Table II).

Blood sugar levels were within normal limits in nine of the eleven patients studied. Slight, transient hypoglycemia was observed in the two others. The blood urea nitrogen content was greatly elevated in only one patient. It was slightly elevated in seven and normal in the others.

The serum electrolytes were mildly deranged in many instances. Hyponatremia and hypochloremia occurred in three patients, two of

whom had Laennec's cirrhosis (Cases 13 and 15). In addition, compensatory hypochloremia was observed in seven patients with respiratory insufficiency. Serum potassium levels tended to be elevated or nearly so in the patients with respiratory acidosis. This finding is in keeping with previous observations [40]. Slight hypokalemia was noted in one of the cirrhotic patients (Case 13) and minimal hypomagnesemia in another (Case 15). Serum calcium levels were normal except for a slight elevation in a patient with metastatic cancer (Case 16).

Blood Gas Analyses (Table III). Increased serum levels of carbon dioxide occurred in the patients with inadequate pulmonary ventilation, but not in those with non-respiratory diseases. In fact, decreased serum CO₂ content was observed in one patient with metabolic acidosis (Case 10) and in another with respiratory alkalosis associated with hepatic coma (Case 12). We have not observed asterixis in normal subjects with voluntary respiratory alkalosis or patients with the hyperventilation syndrome.

The pH of the blood was abnormally low in five patients with respiratory acidosis (Cases 2 to 6) and in one with renal decompensation (Case 10). It was abnormally high in two patients with severe liver disease (Cases 14 and 17), in another with leukemia and infection (Case 12)

TABLE III
MISCELLANEOUS DETERMINATIONS

Case No.	Arterial pH	Arterial Oxygen Saturation (%)	Arterial Ammonia Nitrogen ($\mu\text{g./100 ml.}$)	Venous Ammonia Nitrogen ($\mu\text{g./100 ml.}$)	Electroencephalogram (grade)
1	7.41	81*	150	157	I
2	7.36	78†	...	171	III
3	7.22	75†	...	127	II
4	7.24	81*	133	103	III
5	7.34	63*	207	201	I
6	7.26	45*	173	144	III
7	7.49	77*	164	141	III
8	7.39	98†	153	114	II
9	7.36‡	84-92†	...	121	IV
10	7.24	82†	110	71	III
11	7.40	96*	145	136	Fast
12	7.49	...	144	94	III
13	7.42	89*	153	147	II
14	7.45	94†	271	207	IV
15	7.40	90*	199	179	I
16	7.38	94†	...	101	II
17	7.41‡	108	III
Normal	7.38-7.42 7.34-7.38‡	96-100* 92-100†	80-150	60-150	0

* Manometric determination.

† Ear oximeter.

‡ Venous pH.

and, inexplicably, in a fourth with bronchogenic carcinoma, hypoxemia and hypercapnia (Case 7).

Severe hypoxemia was present in all eight patients with respiratory insufficiency. In addition, mild degrees of arterial oxygen unsaturation were present in both patients with Laennec's cirrhosis. This phenomenon has been previously observed in cirrhosis but has not been adequately explained [41,42]. Another patient, an old man with Cheyne-Stokes respiration (Case 9), exhibited a cyclic variation of arterial oxygen saturation which ranged from normal to markedly desaturated levels. Although confusion and asterixis were continuously present, they became exaggerated at the end of each apneic period and persisted for five to ten seconds after the oxygen saturation had begun to rise toward normal. A similar lag period between local anoxia and electroencephalographic changes has been noted in animal experiments [43]. Short periods of oxygen administration did not alter the sensorium, neurologic abnormalities or electroencephalographic patterns in six of these patients (Cases 2, 5, 8, 9, 12, and 13).

Venous ammonia levels were increased in only five patients and in only one was it greatly elevated. This patient (Case 14) had hemochromatosis and impending hepatic coma which apparently was precipitated by a high protein diet. Several patients with chronic pulmonary insufficiency had either high-normal or slightly elevated blood ammonia values. One of these patients (Case 4) had received acetazoleamide and another (Case 5) had received both acetazoleamide and chlorothiazide. Either of these drugs may interfere with ammonia metabolism and may cause increased ammonia levels [5-8,44,45]. Almost invariably the arterial ammonia levels were higher than venous ammonia concentrations in both patients with hepatic disease and those without.

Liver Function Tests (Table IV). The patients with liver disease had abnormal serum bilirubin, bromsulphalein retention and alkaline phosphatase. These tests were essentially normal in the patients without hepatic disease except for increased bromsulphalein retention in patients with congestive heart failure. Serum albumin concentrations were decreased in both hepatic

TABLE IV
LIVER FUNCTION TESTS

Case No.	Serum Bilirubin (mg./100 ml.)		Brom-sulphalein Retention (%)	Cephalin Flocculation		Thymol Turbidity (units)	Alkaline Phosphatase (Bodansky units)	Serum Protein (gm./100 ml.)		
	1 min.	30 min.		24 hr.	48 hr.			Total Protein	Albumin	Globulin
1	18	0	±	0.3	3.3
2	0.21	0.64	3*	4+	4+	0.2	4.2	5.1	2.0	3.1
3	...	0.55	...	0	0	1.1	2.6	7.5	3.0	4.5
4	...	0.4	...	2+	3+	0.2	2.9	6.3	3.4	2.9
5	...	1.2	...	2+	3+	0.8	5.9	5.9	2.7	3.2
6	6.8	2.9	3.9
7	...	0.25	...	0	0	0.4	6.1	5.9	3.0	2.9
8	1.0	2.0	20*	2+	3+	4.9	3.1	5.9	2.7	3.2
9	0.32	1.4	28	1+	2+	1.6	5.6
10	...	0.7	...	±	1+	1.1	2.3	6.0	2.6	3.4
11
12	...	0.1	...	0*	0*	0.2*	4.2*	5.2	3.1	2.1
13	16.0	25.8	47*	4+	4+	0.8	9.6	6.1	2.1	4.0
14	0.3	1.7	43	1+	2+	4.9	2.1	6.7	1.9	4.8
15	3.4	6.9	58*	0	1+	3.5	14.4	6.4	2.4	4.0
16	...	3.3	65	2+	3+	1.5	11.0	5.5	2.2	3.3
17	4.0	6.0	...	0	0	0.3	20.0
Normal	<0.4	<1.2	<6%	<2+	<3+	0-5	1-5	6.0-8.2	3.5-4.5	2.2-3.7

* Subsequent determination.

and non-hepatic patients, although lower values were found in the group with liver disease. Serum globulin levels were slightly higher in the hepatic patients.

Electroencephalography (Table III, Fig. 1). The electroencephalograms, with a single exception, showed a diffusely slow, non-specific pattern which was similar in the hepatic and non-hepatic groups. The electroencephalogram of the patient with glutethimide intoxication (Case 11) showed almost continuous 18 to 25 cycles per second activity.

COMMENTS

The pathogenesis of hepatic coma and other comatose states is not entirely clear. Although most cases of impending hepatic coma are attributed to ammonia intoxication, this explanation does not satisfactorily explain all cases of this syndrome. Indeed, an indistinguishable picture may be precipitated in patients with hepatic disorders by a number of medications or metabolic abnormalities which are not associated with high blood ammonia levels. Similarly, impaired consciousness in uremia, pulmonary insufficiency and other types of coma is not fully

understood. A more complete understanding of the mechanism of asterixis, which occurs in both hepatic coma and in these other disturbances of consciousness, may clarify our concepts of these disorders.

The present group is comprised of patients with a variety of clinical disturbances in whom delirium and asterixis were observed. An analysis of the laboratory determinations which may be important in the pathophysiology of this syndrome appears to be a logical step in its evaluation.

The concentration of blood ammonia is of obvious interest in this syndrome, since ammonia is of primary importance in the pathogenesis of hepatic coma. In only one patient, who had cirrhosis with classic protein-induced impending hepatic coma, was the blood ammonia markedly increased. Slight elevations were also found in some of the patients with severe cardiopulmonary disorders. This has been observed previously in patients with pulmonary disease [16,17,46] and may be associated with cardiac failure which frequently accompanies it [47]. The performance of ammonia tolerance tests (3 gm. ammonium chloride administered orally)

did not alter the neurologic picture in two of these patients (Cases 8, 9). Although ammonia-liberating compounds can cause this syndrome, it is apparent that neither such substances, nor high blood ammonia levels are essential to its production.

Hypercapnia has been thought by some to be responsible for the neurologic status in carbon dioxide narcosis [16,48,49]. In this syndrome, however, it is difficult to delineate the effects of hypercapnia, anoxia, acidosis and increased intracranial pressure [50-55]. Each of these disturbances is present in chronic ventilatory insufficiency, and each is individually capable of altering brain metabolism and function. Neuromuscular abnormalities similar to those observed in carbon dioxide narcosis may be induced by the inhalation of carbon dioxide [48]. In our series of patients, however, the carbon dioxide content of the blood ranged from abnormally low to abnormally high values. Similarly, the hydrogen ion concentration of the blood varied from severely acidotic to alkalotic. In one patient (Case 3) asterixis and confusion persisted despite gradual correction of the pH from 7.22 to 7.40. These results showed clearly that there is no single abnormality of the carbon dioxide content, of the pH, or of related physicochemical alterations which can be incriminated as the cause of the disorder in all of these patients.

Arterial oxygen unsaturation was demonstrated in many of the patients in this series, but it was not invariably present. Although it is certainly possible that hypoxia *per se* may give rise to the syndrome of delirium and asterixis, it is clear that hypoxemia is not the primary abnormality in all of these patients.

Only two derangements of the serum electrolytes, hypokalemia and hypomagnesemia, have previously been directly associated with asterixis [14,18]. Low serum potassium levels were observed in one of our cirrhotic patients and low magnesium levels in another. Both of these electrolyte abnormalities are commonly seen in patients with alcoholic cirrhosis [56,57]. In neither of these patients did other clinical or laboratory findings indicate a profound depletion of these substances. We have observed asterixis, however, in other patients in whom hypokalemic metabolic alkalosis was the primary disorder. Although serum electrolyte patterns were frequently abnormal in these patients, in none were they sufficiently deranged to attribute the neurologic disturbance to them.

Hypoglycemia, which may mimic hepatic coma, has been observed both in primary liver disease [58] and in congestive hepatomegaly [59]. Minimally low blood sugar levels were observed transiently in two of our patients but they did not appear to be clinically significant in either.

Uremic coma may also simulate impending hepatic coma [14,19,20]. Although the blood urea nitrogen was elevated in eight patients, only one patient (Case 10) had renal decomposition of the degree ordinarily associated with the symptoms of uremic coma.

All of the electroencephalographic tracings except one showed diffusely distributed high voltage slow waves. This pattern is characterized by bilateral synchronous delta and theta waves of increased voltage which progressively replace the normal alpha rhythm. Indistinguishable tracings occur in hepatic coma [14,20,24], pulmonary insufficiency [16,25], uremia [20,25], congestive heart failure [25] and sometimes in deep sleep [60,61]. Similar patterns have been observed in anemia [25], hypoglycemia [61-63], hypokalemia [20,24], Addison's disease [64], hypothyroidism [65,66], alcoholic intoxication [25,61], bromism [27], increased intracranial pressure [20,61] and other diffuse cerebral diseases [20,24,25]. Similar tracings have been induced in normal subjects by anoxia [64,67] or hypercapnia [49,68] and in cirrhotic patients by the administration of ammonium salts [69], methionine [20] or chlorothiazide [6-8]. Triphasic waves, which have been thought to be almost pathognomonic of hepatic coma [23,24], were observed in some of our patients with both hepatic and non-hepatic diseases.

The electrical activity of the brain as recorded in the electroencephalogram parallels the functional integrity of the brain [25,66]. Each of the disorders discussed results in impairment of cerebral metabolism which is reflected by slowing of the electroencephalographic pattern. Some investigators believe that these slow records represent decreased oxygen utilization [20] and it has been shown that in hypoglycemia a fall in cerebral oxygen consumption accompanies the appearance of delta waves [63]. The electroencephalogram may actually register a decrease in frequency before the less sensitive measurement of cerebral oxygen consumption falls and even before mental symptoms are noted [66]. Correction of the metabolic defect usually causes the mental state and the electroencephalogram to revert to normal [64]. Although the

absolute frequency of the electroencephalogram is not proportional to the disturbance of consciousness, the degree of slowing is thought to serve as a reliable index of cerebral insufficiency in the individual patient [66]. Our findings support this concept.

The patient with glutethimide intoxication had a tracing which showed almost continuous, fast activity. An increase in the frequency of the electroencephalogram may occur during fever [70], after the administration of thyroxine [71], quinacrine [66], dinitrophenol [71], and in barbiturate intoxication. The explanation for the fast activity in these situations is not clear. The fast activity in this patient was thought to be analogous to the pattern seen with other sedative drugs.

Although the failure to identify a specific biochemical abnormality common to all these diseases does not exclude such an abnormality, it seems unlikely that the same basic metabolic aberration occurs in each of these diseases. It appears more likely that these diverse disorders may each interfere with a fundamental metabolic pathway at a different point, depending on the nature of the primary disease.

Attention was first focused on anoxia as the responsible factor by several clinical observations. The first of these was made in a patient without disease of the liver in whom lethargy and unilateral right-sided asterixis were observed. This phenomenon persisted for more than thirty hours until a right hemiplegia developed as a result of a cerebral infarction. This suggested that the hemiasterixis may have represented localized anoxia of the brain. Subsequently, a patient with Cheyne-Stokes respiration (Case 9) was observed to have delirium and asterixis which were more marked at the end of each apneic period. These fluctuations again suggested that anoxia may have been responsible for the neurologic picture. Further support for this concept was derived from the observation that asterixis may disappear after the administration of oxygen [75].

The brain derives its energy primarily from the oxidation of glucose. Insufficiency of this substrate or of the oxygen required for its combustion, or interference with the enzymes which catalyze its degradation impair this process and give rise to functional disturbances. Cerebral insufficiency may thus arise from hypoglycemic or hypoxemic states or circulatory disorders. Many drugs such as alkaloids, bromides or

aliphatic depressants reversibly block these enzyme systems. Although the exact mechanisms are unknown, uremia and hepatic coma are thought to interfere with enzyme-catalyzed reactions. Most comatose states have been attributed to decreased cerebral oxygen utilization and this has been demonstrated in hepatic coma [28,29], uremia [30,31], diabetic coma [72], alcoholic intoxication [32], barbiturate intoxication [32], cerebral arteriosclerosis [34,35] and hypoglycemia [73,74]. Although cerebral oxygen consumption in chronic pulmonary insufficiency is not greatly reduced [75], there is little doubt that cerebral anoxia is of major importance in this syndrome.

It is apparent that the disease processes in which asterixis occurs are the same delirious states in which decreased cerebral oxygen consumption and diffusely slow electroencephalograms co-exist. These relationships indicate that arterial hypoxemia is not the sole cause of these syndromes, but rather that it is merely one of many abnormalities which depress brain metabolism. It follows that any disease, drug or alteration of the internal environment which interferes with the metabolic processes of the brain may give rise to cerebral insufficiency and perhaps to asterixis.

The neurologic mechanism responsible for this syndrome is unknown. Is it conceivable that depression of the reticular formation of the central nervous system could account for the neurologic picture seen in these patients?

The ascending reticular system performs innumerable integrative functions of the nervous system, and is especially concerned with the maintenance of wakefulness, the focusing of attention and the integration of sensory impulses [76]. The role of the descending reticular system is not as well defined, but it is important in the maintenance of muscle tone and posture and in the coordination of motor activity [76-79].

Substances such as barbiturates and ether apparently produce anesthesia by causing a reversible functional block of the ascending reticular system [80-82]. Anoxia [81], hypoglycemia [80,81], or hypercapnia [83] may also selectively suppress reticular function, and induce non-specific slowing of the electroencephalogram in animals. The inhalation of high concentrations of carbon dioxide may give rise to rhythmic movements of the extremities [48] and may influence the deep tendon reflexes [84]. In addition, some ataractic compounds,

such as chlorpromazine derivatives, which appear to influence the reticular formation, may give rise to muscular rigidity, Parkinsonian-like tremor [85] and bizarre motor disturbances [86,87]. The neuromuscular abnormalities which accompanied asterixis in our patients are not dissimilar to those induced by experimental excitation or inhibition of the descending reticular formation.

It is conceivable that the impaired consciousness, asterixis and other neuromuscular phenomena observed in various types of metabolic and toxic coma may be mediated by interference with the reticular formation. Effects on other, non-reticular neural pathways cannot be excluded.

The relationship of infection and fever to this syndrome also deserves comment. Two patients (Cases 10 and 12) had septicemia and a high fever at the time the flapping tremor was present. In one of these patients (Case 12) the delirium and asterixis persisted for only a brief period and closely paralleled the temperature curve. It recurred in this patient several months later, again associated with the fever of another infection.

The explanation for the induction of this syndrome by drugs with various pharmacologic properties is not clear. After the administration of acetazoleamide, for example, drowsiness and sleep may occur in normal persons. In cirrhotic patients, however, confusion and asterixis are sometimes precipitated. With the administration of chlorothiazide, impending hepatic coma appears to be associated with a good diuretic and kaliuretic response, and seems prone to develop in those persons who have previously experienced impending hepatic coma [6]. It was suggested that the brains of patients who have recovered from impending hepatic coma might be more sensitive to many metabolic abnormalities, including hypokaliemia [88].

Sherlock [88] has emphasized that the clinical picture of hepatic coma is a non-specific one which may be simulated by many other disturbances. Several of these have been discussed here. This syndrome may be seen in otherwise normal persons with major metabolic derangements or after the administration of large doses of sedative or narcotic drugs. In patients with underlying disease of the liver relatively mild metabolic abnormalities or small doses of these compounds may precipitate this syndrome, suggesting that these patients are peculiarly

susceptible to metabolic insults. The induction of identical neurologic signs by similar abnormal stimuli in patients with pulmonary, cardiac or renal disease broadens this hypothesis. It is probable that in such patients the brain is particularly susceptible to metabolic or toxic derangements.

SUMMARY

Asterixis, the flapping tremor, while characteristically seen in hepatic coma was observed in twelve patients without primary disease of the liver. All of these patients, who had chronic pulmonary insufficiency, arteriosclerotic cardiovascular decompensation, uremia or other disorders, exhibited delirium of varying severity. Five additional patients with underlying hepatic disease and impending hepatic coma, each precipitated in a different manner, were also studied.

Arterial hypoxemia was found in the majority of these patients, but was not uniformly present. Serum electrolytes, carbon dioxide content, blood ammonia concentration and hydrogen ion concentration were not consistently abnormal. Liver function studies were essentially within normal limits in the patients without disease of the liver. Electroencephalographic patterns were diffusely and non-specifically slow except for the patient with glutethimide intoxication, in whom it was abnormally fast.

Asterixis appears to be a non-specific neurologic finding which may accompany organic delirium in a variety of metabolic or toxic disorders which interfere with cerebral metabolism.

The similarity between the clinical findings in these patients and experiments in animals suggests that asterixis may result from metabolic interference with the function of the reticular formation of the central nervous system.

The brain of patients with chronic hepatic, cardiac, pulmonary and renal diseases may be particularly sensitive to metabolic or toxic disturbances.

APPENDIX

CASE REPORTS

CASE 1. J. P., a sixty-seven year old man who had a long history of pulmonary emphysema, fibrosis and inactive tuberculosis, was admitted to the West Haven Veterans Administration Hospital with severe dyspnea, following an upper respiratory infection. The patient had dyspnea and cyanosis and, although very apprehensive, he was grossly oriented. He had emphysema of the chest and diffuse expiratory wheezes

and rales were audible. There were no signs of congestive heart failure. Neurologic examination was within normal limits except for asterixis and a left extensor plantar reflex. There were no stigmas of hepatic disease, and fetor hepaticus could not be detected. The neurologic abnormalities disappeared on the sixth hospital day as the patient improved on therapy with antibiotics, intermittent positive pressure breathing and bronchial dilators.

CASE 2. E. P., a sixty-four year old Negro with chronic asthmatic bronchitis and secondary emphysema was admitted to the Grace-New Haven Community Hospital in deep coma. His respirations were shallow and irregular, and he was deeply cyanotic. His chest was hyperresonant, and decreased breath sounds and scattered coarse moist rales were audible. Clubbing of fingers was prominent. His cervical veins were distended, but there were no other signs of cardiac or hepatic disease. Tracheotomy was performed and respiration was supported in a tank respirator. Levarterenol was administered for forty-eight hours to maintain blood pressure at normal levels. Asterixis was noted on the third day, after he had begun to improve. He was awake and oriented as to person and place, but drowsiness persisted. Neurologic examination was otherwise within normal limits. There was no fetor hepaticus. The flapping tremor persisted for four days at which time the biochemical studies were performed.

CASE 3. O. C., a sixty year old man, with pulmonary emphysema and fibrosis, was admitted to the West Haven Veterans Administration Hospital with progressive fever, dyspnea and confusion, secondary to an upper respiratory infection. His vital signs were normal except for a low grade fever. He was lethargic, intermittently confused and deeply cyanotic. His respirations consisted of short inspiratory gasps and prolonged expiration. His chest showed increased anteroposterior diameter, hyperresonance, inspiratory and expiratory wheezes and rales. There were no clinical signs of cardiac or hepatic disease. The retinal veins were engorged and the medial disk margins were blurred. Neurologic examination was within normal limits although the patient was not examined for asterixis. Oxygen was administered intermittently and luminal was given for sedation after which the patient became stuporous. At the time asterixis was noted, the arterial pH was 7.22. Asterixis persisted for four days without other neurologic abnormalities, and was still present after his arterial pH had returned to normal. Therapy consisted of antibiotics, intermittent positive pressure breathing, and the use of bronchodilators.

CASE 4. W. C., a sixty-eight year old man with pulmonary emphysema and fibrosis, cor pulmonale, and arteriosclerotic cardiovascular disease, was admitted to the West Haven Veterans Administration

Hospital with increasing dyspnea and somnolence of one week's duration. During this period he had received therapy with digitalis, acetazoleamide, phenobarbital and promazine (Sparine®). The patient was deeply cyanotic and he exhibited tachypnea and tachycardia. He had emphysema of the chest and showed decreased breath sounds and basilar rales. Cardiomegaly and ankle edema were present. He was disoriented. Except for depressed deep tendon reflexes, generalized weakness and the flapping tremor, his neurologic examination was within normal limits. Treatment with antibiotics and intermittent positive pressure breathing resulted in gradual improvement. The flap persisted for forty-eight hours.

CASE 5. J. S., a fifty-six year old man, was known to have chronic pulmonary insufficiency and fibrosis with cor pulmonale. Progressive shortness of breath was treated with acetazoleamide and chlorothiazide by his physician. He had severe headache, twitching of the extremities, and somnolence for which he was admitted to the West Haven Veterans Administration Hospital. He was drowsy, but on awakening appeared normally oriented. Asterixis, which was the only significant neurologic abnormality, persisted for about forty-eight hours. His fundi showed engorged retinal veins but no papilledema. His chest was kyphotic. The breath sounds were diminished with prolonged expiratory phase and crackling inspiratory rales. The heart size was not increased. The liver was palpable 5 cm. below the right costal margin. Treatment, which consisted of oxygen, phlebotomy and digitalis, resulted in rapid improvement.

CASE 6. J. M., a sixty-two year old man with an inoperable carcinoma of the upper lobe of the right lung, was admitted to the hospital because of cough, back pain and rib pain. Shortly prior to admission he had had an episode of confusion after which an electroencephalogram showed a left temporal lobe focus compatible with a cerebral metastasis. Except for signs of an extensive tumor of the right upper lung field, physical examination was within normal limits. One month after admission he was found in a semistuporous state, deeply cyanotic, with stertorous respiration presumably due to airway obstruction due to the aspiration of secretions. He gradually became normally alert although he appeared euphoric. Asterixis was present. The right pupil was smaller than the left, but other neurologic findings were within normal limits. The patient died quietly twenty-four hours later. Autopsy showed an oat cell carcinoma which had metastasized extensively. There was a 2 by 2 cm. tumor replacing the right posterior clinoid process but there were no other intracranial metastases present.

CASE 7. R. C., a sixty-six year old man with metastatic epidermoid carcinoma of the right upper

lobe, was admitted to the West Haven Veterans Administration Hospital. Dullness and diminished breath sounds over the right upper part of the chest and hepatomegaly were the only abnormalities noted. Staphylococcal pneumonia developed and he became severely dyspneic and cyanotic. A series of shifting cardiac arrhythmias complicated the picture. As his condition grew worse, he became progressively more cyanotic and confused. Asterixis was noted, and it persisted until he died several days later. No other neurologic phenomena were detected. No autopsy was performed.

CASE 8. M. W., a sixty-three year old man, had hypertensive arteriosclerotic cardiovascular disease and cardiac decompensation for approximately seven years. The patient, in whom nocturnal disorientation and intermittent diurnal confusion had developed was admitted to the West Haven Veterans Administration Hospital because of these symptoms. Mild jaundice and fever developed in relation to the administration of meprobamate. A biopsy specimen of the liver showed chronic passive congestion. Asterixis was first noted at this time without other neurologic abnormalities. The flapping tremor was intermittently present until the patient's death about six months later. A moderate degree of urea retention was present throughout this period. Serial electroencephalograms showed abnormally slow patterns. Neither the mental state nor the electroencephalographic patterns were altered by the administration of oxygen. Many blood ammonia levels were normal and an ammonia tolerance test had normal results. Autopsy showed severe generalized arteriosclerosis with severe involvement of the vessels of the brain and heart. Multiple myocardial infarctions were found. The liver showed pericentral atrophy secondary to chronic passive congestion.

CASE 9. A. B., an eighty-three year old man, had hypertensive arteriosclerotic cardiovascular disease and cardiac decompensation for eight years. The patient had been admitted to the West Haven Veterans Administration Hospital for anginal pain and paroxysmal supraventricular tachycardia. Cheyne-Stokes respiration was present. Signs of congestive heart failure were apparent. The patient, throughout the hospital course, was drowsy and would periodically lapse into light sleep. He was usually combative and unreasonable. He was oriented only to his own identity. Approximately two weeks after admission persistent asterixis was first noted. There were no other neurologic abnormalities except for fasciculations of the muscles of both forearms and involuntary twitchings of the extremities near the end of each apneic period. The flapping tremor, which was present throughout the cycle, was more severe at the end of the prolonged apneic period. Arterial oxygen saturation varied from 83 to 92 per cent by ear

oximetry. The most severe asterixis occurred from five to ten seconds after the lowest oxygen saturation was recorded. An ammonia tolerance test had normal results and did not exaggerate the severity of the flapping tremor. The patient suddenly died several months after admission. Autopsy showed generalized arteriosclerosis with especial involvement of coronary and cerebral arteries. Old infarcts were found near the left internal capsule and in the right cerebellar cortex. Atrophy of the gyri and widening of the sulci were present. The liver showed chronic passive congestion.

CASE 10. W. C., a sixty-one year old man, was known to have bilateral bronchiectasis. He was admitted to the West Haven Veterans Administration Hospital with gradually progressive shortness of breath and fever. Dullness to percussion, rhonchi, and musical rales were present bilaterally. There was no evidence of cardiac or hepatic disease. The patient showed clubbing of the fingers, but he was not cyanotic. Neurologic examination was within normal limits. Asterixis was not present. The patient received therapy with penicillin, chloramphenicol and streptomycin without change in the fever. The blood urea nitrogen was found to be 172 mg. per 100 ml. On the twelfth hospital day the patient was drowsy and lethargic although he remained well oriented. Asterixis was noted without other neurologic abnormalities or fetor hepaticus. These findings persisted until the patient died two days later. Post-mortem examination showed severe bilateral bronchiectasis of the lower lobe of the lung with an extensive acute pneumonitis. The kidney showed a severe acute necrotizing glomerulitis, presumably embolic in origin.

CASE 11. W. F., a twenty-three year old student, was admitted to the West Haven Veterans Administration Hospital in deep coma after having ingested 5 gm. of glutethimide (Doriden®) in an attempt at suicide. On admission to the hospital, physical examination was within normal limits except for a blood pressure of 80/55 mm. Hg, absent deep tendon reflexes, and bilateral extensor plantar reflexes. He received levarterenol for several hours to maintain normal blood pressure. Twenty-four hours later he was drowsy but awake, oriented as to time and person, and spoke incoherently. Neurologic examination was within normal limits except for asterixis which was more severe on the right, dysdiadochokinesis, and ataxia. The Babinski reflexes were no longer present. The electroencephalogram showed continuous eighteen to twenty-five per second activity with many sharp wave discharges. Twenty-four hours later all clinical signs had subsided.

CASE 12. J. B., a seventy-one year old patient at the West Haven Veterans Administration Hospital, had chronic lymphatic leukemia. A urinary tract in-

fection and bacteremia due to *Pseudomonas aeruginosa* developed. On the fifth day of the bacteremia, at a time when his temperature was 105°F., a flapping tremor was noted. Although the patient was fully oriented he was apprehensive and agitated and his span of attention was very short. Neurologic examination was otherwise within normal limits. He was receiving prednisone at this time, and prophylactically isonicotinic hydrazide for an old, apparently inactive tuberculosis infection; chlortetracycline and parenteral neomycin were also administered for the bacterial infection. About six hours later, the temperature had dropped to 102°F. Although his mental state was unchanged, the flap was barely detectable. Twelve hours thereafter the patient, who was afebrile, was normal mentally, and the asterixis could no longer be elicited. Serial electroencephalograms showed a return toward normal over several days.

CASE 13. R. S., a forty year old alcoholic with decompensated Laennec's cirrhosis, was admitted to the West Haven Veterans Administration Hospital with pneumococcal pneumonia. Although the pneumonia responded to antibiotic therapy, the severity of the hepatic disease progressed and recurrent bleeding from hemorrhoids occurred. Progressive confusion, disorientation, fetor hepaticus, and asterixis developed. At examination no other neurologic abnormalities were revealed. Despite blood transfusions, the administration of neomycin and cessation of the intake of protein, he became anuric, deeply comatose and died.

CASE 14. W. H. F., a sixty-four year old man with hemochromatosis, was admitted to the West Haven Veterans Administration Hospital with impending hepatic coma apparently following administration of a high protein diet. On admission he was somnolent and grossly disoriented as to time, place and person. A flapping tremor was present. He had a mild pill-rolling tremor at rest. Dysdiadokokinesia was present, but no other neurologic abnormalities. Slight jaundice was present as was palmar erythema and hepatosplenomegaly. Fetor hepaticus was not detected. On elimination of protein from the diet and the administration of neomycin orally, his mental state improved. Within three days the asterixis had disappeared, the elevated blood ammonia had returned to normal, and the electroencephalogram which had abnormal results had shown improvement.

CASE 15. J. C., a thirty-nine year old man with alcoholic cirrhosis and a traumatic left hemiparesis, was admitted to the West Haven Veterans Administration Hospital with persistent bleeding from a facial laceration. He was dehydrated, hypotensive and deeply jaundiced on admission. Asterixis and mental sluggishness fluctuated in severity for three weeks and then became progressively worse. It was found subse-

quently that he had been surreptitiously taking an unknown number of Sominat® tablets (chloral hydrate and antipyrine) for "nervousness" for about ten days preceding the aggravation of these signs. At the time the studies were performed his speech was incoherent and his manner intoxicated. He was oriented as to his own person but only vaguely to his environment. Neurologic examination showed only diminished deep tendon reflexes and a Babinski reflex on the left. Treatment which consisted of the administration of neomycin, elimination of protein from the diet and discontinuation of the hypnotic drug, resulted in progressive improvement. A biopsy specimen of the liver showed Laennec's cirrhosis with massive fatty infiltration, and active necrosis.

CASE 16. R. J., a sixty year old man with metastatic cholangioma, was admitted to the West Haven Veterans Administration Hospital for terminal care. The patient was jaundiced, exhibited palmar erythema, spider angiomas, ascites, abdominal collateral veins and hepatomegaly. He was well oriented. Neither fetor hepaticus nor flapping tremor was detected on admission. Two weeks later the patient had become lethargic, although he remained fully aware of his surroundings. Asterixis was detected at this time and persisted until his death three weeks later. Chloral hydrate, 1 gm. daily, was the only medication he was receiving before the appearance of the flap. The neurologic examination was otherwise non-contributory. Fetor hepaticus was not present. Autopsy revealed extensive metastatic cholangioma. There were many areas of infarction in the liver, but there was no evidence of cirrhosis. The brain was not examined.

CASE 17. F. C., a thirty-six year old man, was admitted to the West Haven Veterans Administration Hospital for terminal care for metastatic seminoma. During hospitalization he had continuous pain in the epigastric right upper areas of the abdomen, an enlarging, nodular liver, and subsequently, jaundice. Chlorpromazine which had been administered for several months was discontinued when the jaundice appeared. Prochlorperazine (Compazine®) and dextropropoxyphene (Darvon®) were employed. After one week of this therapy the patient became lethargic and mentally obtunded. Asterixis appeared without other neurologic findings. The administration of prochlorperazine was discontinued without altering any other medication. The patient's mental state progressively improved and the flapping tremor disappeared within thirty-six hours, accompanied by improvement in the electroencephalogram. When prochlorperazine was again administered confusion and asterixis reappeared. The patient died two weeks later. Autopsy revealed extensive metastatic involvement of the liver.

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The FII Agglutinating Factors in Serums of Patients With Non-Rheumatic Diseases*

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CUMULATIVE studies on the rheumatoid agglutinating factor (RAF) suggest an immunologic disturbance and a possible linkage of the factor to the pathogenesis of rheumatoid arthritis [1]. An important unanswered question is whether RAF is produced primarily in the abnormal metabolic processes of rheumatoid arthritis and closely related disorders or whether RAF may be evoked more broadly by various unrelated diseases.‡ Positive agglutination reactions measured by various serologic methods have been reported at incidence levels of 70 to 95 per cent in patients with rheumatoid arthritis [2-7], whereas only 1 to 3 per cent levels of positivity have been found in the majority of control populations [8]. However, by selection of patients for tests, based on a diagnosis of certain non-rheumatic diseases, the frequency of false positive agglutinating serums is greatly increased. Thus Kunkel, Simon and Fudenberg [9] found positive tests for RAF in six of sixty-one patients with disseminated sarcoidosis and Peltier and Christian [10] noted 11 per cent positive Cohn's fraction II (FII) tanned sheep cell tests in 140 patients with syphilis. In febrile illnesses [11] and virus infections [12] positive serologic reactions for RAF were encountered. Cobb, Lincoln and Lincoln [13] observed a surprisingly high number of positive euglobulin latex tests in patients with peptic ulcer and essential hypertension during a population survey. The over-all frequency of positive reactions for

RAF in patients with hepatitis was 16 to 30 per cent in various reports [8,12,14].

The following study provides data on positive RAF reactions in patients with hepatic disease and some other disorders. Also included are the results of serologic and physical-chemical studies on serums from six patients with low or moderate agglutinating titers in FII-reactant systems. It is noteworthy that the agglutinating factors in serums of patients with non-rheumatic diseases were similar, in those parameters measured, to RAF of rheumatoid origin.

CLINICAL MATERIAL AND METHODS

From January, 1956 to April, 1959, serums were collected from 207 patients with acute and chronic non-rheumatic diseases on the medical and surgical wards of Jackson Memorial Hospital. The serums, stored at minus 20°C., were subjected at intervals to serologic tests for RAF. A retrospective hospital record analysis was made. Of the patients with positive serologic reactions, those available were recalled for studies on fresh serum.

The original Singer-Plotz (direct latex) test [2] was used for screening, as well as in the special studies. Additional or substitute tests for RAF were employed only if specifically mentioned. These include the FII sheep cell (FII SC) test of Jacobson et al. [4], the sensitized sheep cell agglutination test (SSC) of Rose et al. [15] and a "modified euglobulin" latex test [16]. In the last test, euglobulin fractions prepared with dilute hydrochloric acid according to the method of Erickson et al. [17], were subjected to the latex procedure of Hall et al. [18]. Precipitin curves using Cohn's fraction II and fresh, whole serum were performed as described by Christian [19], with nitrogen determinations by the Markham modification of the Kjeldahl method [20]. Euglobulin prepared by dialysis (Ziff et al. [5]) was used for precipitin curves performed as reported by Epstein, Johnson and Ragan

‡ RAF as employed here refers collectively to one or all of the human serum factors reactive with human or heterologous sensitizing globulins in FII sheep cell test, FII latex, sensitized sheep cell agglutination test, human RH⁺ and the other agglutination systems described by Ziff [8].

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TABLE I
AGGLUTINATION TESTS ON SERUMS OF TWO HUNDRED AND SEVEN PATIENTS WITH NON-RHEUMATIC DISEASE (JANUARY 1956 THROUGH APRIL 1959)

Group A (liver damage)			Group B (miscellaneous)		
Disorder	Total No. of Patients Tested	Patients with Positive Test Results*	Disorder	Total No. of Patients Tested	Patients with Positive Test Results*
Acute hepatitis	10	3	Malignant tumors	16	3
Portal cirrhosis	23	7	Leukemia	4	2
Chronic hepatitis	2	2	Chronic pyelonephritis	4	1
Biliary lithiasis	6	1	Chronic pancreatitis	2	1
Congestive hepatomegaly	2	1	Chronic cholelithiasis	4	1
			Adrenocortical adenoma	1	1
			Chronic idiopathic thrombo- phlebitis	1	1
			Other diseases	132	0
Total	43	14 (32.6%)	Total	164	10 (6.1%)

* FII Latex or FII Sheep Cell Agglutination.

[27]. Fresh, whole serum was subjected to cold precipitation by the technic of Svartz and Schlossmann [22]. Analytical ultracentrifugation was employed on fresh, whole serum as well as "sucrose fractions" using a Spinco Model E Ultracentrifuge. The sucrose fractions were prepared by density gradient ultracentrifugation according to the method of Franklin *et al.* [23], modified as follows: (1) 1.5 ml. samples of fresh, whole serum were layered over 2 ml. of 37 per cent sucrose in plastic tubes and rotated in a swinging bucket rotor at 32,500 revolutions per minute for four hours using a Spinco Model L Ultracentrifuge; (2) the bottom gelatinous fraction and two upper layers of liquid supernate were removed with a Spinco tube slicer; and (3) sucrose fractions were dialyzed against buffered saline solution (pH 8, $\mu = .16$) and subsequently divided, a portion being used for direct latex tests and the remainder for analytical ultracentrifugation. Sedimentation constants were corrected to zero concentration, and protein content represented by the schlieren peaks were calculated from planimetric measurements together with a refractive index determination [24-28]. Continuous-recording ultraviolet spectrums were obtained on the ultracentrifuged fractions with a Beckman DK-2 spectrophotometer.

RESULTS

Clinical Survey. Fourteen of the forty-three patients with hepatic disorders and ten of 164 patients with miscellaneous diseases had positive FII SC and direct latex tests. (Table I.) The

majority of patients with liver disease and positive agglutination tests suffered from acute viral hepatitis or portal cirrhosis. In the non-hepatic disease group, malignant tumors and leukemia accounted for positive agglutination reactions in half of the patients. In a third group of 200 patients with osteoarthritis, non-articular rheumatism and gout there were 3 per cent positive reactions (unpublished observations).

A survey of liver function tests on patients with positive serologic reactions is shown in Table II. At the bottom of the table are data on two patients of Group B (A. Pr. and J. L.) without liver disease, included because of special studies. Among the fourteen with hepatic disorders, six were males. Their ages ranged from eighteen to eighty-four years. The frequency of positive agglutination reactions in this small series was divided equally between patients with viral hepatitis and cirrhosis, the types of cirrhosis being portal, cardiac, postnecrotic and biliary. Except for two patients (S. B. and B. W.), suffering from duodenal ulcer and sickle cell anemia, respectively, no other serious active disease was detected. Follow-up studies necessitated by positive heterophil agglutination tests in one patient (G. F.) and positive reaction to a serologic test for syphilis in a second patient (R. T.) revealed no evidence of infectious mononucleosis or latent syphilis. Results of

TABLE II
HEPATIC FUNCTION AND SEROLOGIC TESTS IN NON-RHEUMATOID PATIENTS WITH POSITIVE FII AGGLUTINATION TESTS

Patient and Sex	Age (yr.)	Tests (Titer)	History of Alcoholism (A) Blood Transfusion (B§)	Presence of Hepatomegaly (H) Ascites (As)	Bilirubin (mg. %)		Thymol Turbidity (units)	Cephalin Flocculation (0-4+48 hr.)	Alkaline Phosphatase (Bodansky units)	Total Serum Protein (gm. per cent)	Globulin (gm. per cent)	Heterophil	Serologic Test for Syphilis	Remarks
					One Minute	Total								
H. J., M	52	1:40*	A	H AS	7.4	14.8	1.0	3+	34.8	4.0	2.0	Negative	Negative	Autopsy: portal cirrhosis
A. B., F	38	1:112†	A	H	9.1	17.2	5.0	4+	10.8	7.4	3.7	...	Negative	Autopsy: marked fatty metamorphosis and early portal cirrhosis
S. L., M	54	1:112†	A	H	0.6	1.0	...	3+	...	5.7	...	Negative	Negative	Autopsy: extensive portal cirrhosis
R. T., M	42	1:112†	AB	H	2.6	4.3	8.0	4+	13.4	6.3	4.5	Negative	Positive	Esophageal varices; clinical diagnosis: portal cirrhosis
B. W., F	18	1:40*	B	H	8.1	14.5	15.6	5.7	3.5	Negative	Negative	Clinical course consistent with serum hepatitis and sickle cell anemia
R. W., M	58	1:448†	B	H	6.0	4+	...	6.8	1.7	Negative	Negative	Clinical course consistent with serum hepatitis; died in hepatic coma
S. B., M	56	1:56†	0	H	4.7	8.0	8.0	2+	11.8	6.1	3.8	Negative	Negative	By clinical course, chronic hepatitis; duodenal ulcer
A. P., M	34	1:224†	0	H	4.1	6.9	10	3+	12.3	5.4	3.9	Negative	Negative	Clinical course consistent with infectious hepatitis
G. F., F	31	1:320†	0	H AS	5.5	9.2	12	4+	5.8	7.5	5.2	Positive	Negative	Chronic hepatitis of unknown etiology
A. M., M	84	1:224†	0	H	6.6	17.7	7.7	4+	19.4	6.7	5.3	Negative	Negative	Acute biliary obstruction, undetermined etiology
A. S., F	56	1:160*	A	H AS	4.5	12.1	2.5	4+	5.5	5.2	3.7	Negative	Negative	Autopsy: portal cirrhosis
P. S., M†	64	1:160*	0	H	0.5	1.5	20	4+	2.5	10.2	6.7	Negative	Negative	Surgical biopsy: portal cirrhosis
E. N., M‡	57	1:80*	A	H	3.0	5.6	...	4+	...	6.4	4.3	Negative	Negative	Cardiac cirrhosis, pulmonary emphysema, fibrosis and cor pulmonale (postmortem)
G. L., F‡	32	1:320*	0	H AS	5.5	9.2	12	4+	5.8	7.5	5.2	Negative	Negative	L.E. preparations positive; postnecrotic cirrhosis at autopsy
A. Pr., F‡	61	1:1280*	0	0	0.07	.28	2.0	Negative	2.0	6.1	2.2	Negative	Negative	Chronic idiopathic recurrent thrombophlebitis; gastrocnemius biopsy negative for arteritis and myositis
J. L., M‡	76	1:1280*	B	0	0.10	0.22	2.0	4+	...	7.0	2.9	Negative	Negative	Pelography together with cylindruria, celluluria and recurrent bacilluria indicative of chronic pyelonephritis

* Indicates that the Fu Latex test performed.

† Indicates that the FuSC test performed.

‡ Patients receiving the special serologic studies.

§ Blood transfusions were given within six months prior to tests.

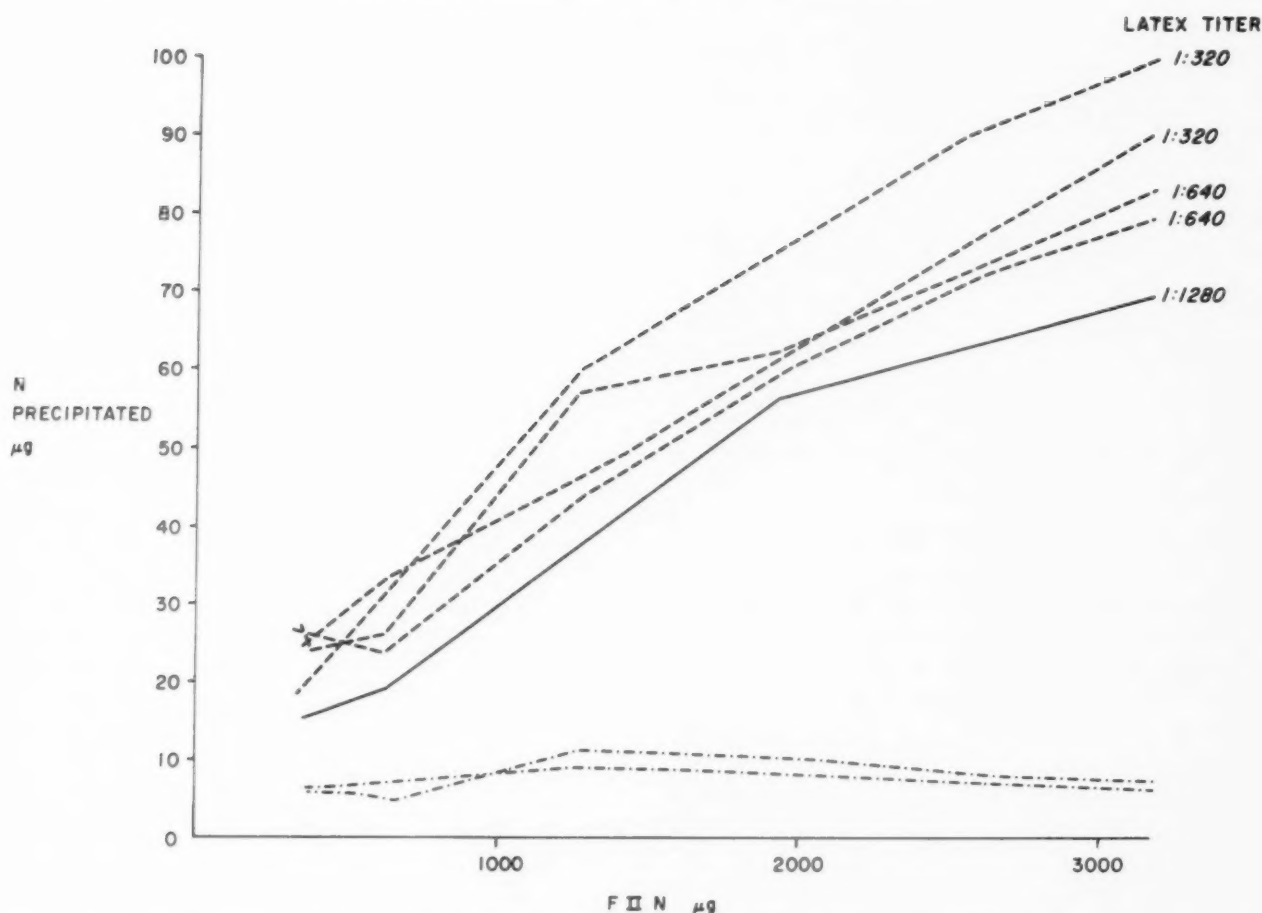


FIG. 1. FII precipitin studies on the serums of four patients with hepatic disease and positive FII latex tests (dashed line), a patient with rheumatoid arthritis (solid line), and two normal subjects (dot-dash line).

L.E. preparations obtained in the sixteen patients were negative, with the exception of one patient (G. L.). Liver function tests were extensively deranged in a manner anticipated for patients with moderate to severe hepatic disease. Positive reactions for RAF were in the low range of 1:224, or less, by the FII SC and 1:160, or less, by the direct latex method.*

Special Serologic Studies. Three of the four patients with hepatic disease (Table II) had jaundice at the time of study, and the diagnosis was confirmed by autopsy or biopsy in all. Three patients with rheumatoid arthritis and three normal subjects served as controls in some experiments. Whole serum precipitin curves were similar in four patients with non-rheumatic diseases and in one patient with rheumatoid arthritis; no distinction of the individual curves in relation to direct latex titers was apparent.

* These levels are lower than encountered in most patients with rheumatoid arthritis at this clinic. The majority with rheumatoid arthritis demonstrate a minimum FII SC titer of 1:896 and direct latex titer of 1:320.

(Fig. 1.) With euglobulin fractions of test serums, the precipitin patterns fell within the range of the serums of patients who suffered from rheumatoid disease. (Table III and [27].) The highest serum dilutions revealing a precipitate occurred with gamma globulin nitrogen levels of 0.53 to 0.13 mg. per 0.5 ml. The serums in two of five patients (E. N. and RA-2) gave bizarre curves.

The specially tested serums were heated to 60°C. in a water bath and removed at intervals over a period of thirty to 120 minutes, with subsequent tests for RAF. (Table IV.) The serums of five patients with non-rheumatic disease had some loss of activity at 120 minutes, but one patient (G. L.) retained a high titer of RAF up to 120 minutes, when congealing occurred. In the serums of all six patients, activity was lost or congealing appeared at 80°C. within a half hour. RAF activity persisted after storage for periods of two to twelve months in each patient except one (A. S.), in whom the titer fell by one tube. Repeated freezing and thawing of serum in two patients (J. L. and E. N.) also had no effect on

TABLE III
PRECIPITIN REACTIONS BETWEEN FII AND EUGLOBULIN
FRACTIONS OF POSITIVE AGGLUTINATING SERUMS

Patient	Maximum Dilution of Euglobulin-Yielding Precipitate*								
A. S.	2	4	8	8	2	1	1	1	1
P. S.	2	4	8	4	4	2	0	0	0
E. N.	4	4	4	4	2	2	2	1	1
G. L.	4	4	8	8	8	4	1	0	...
A. Pr.	16	16	32	8	4	2	0	0	...
J. L.	4	8	4	4	4	4	4	1	1
L. M.†	2	2	4	2	0	0	0	0	0
H. B.†	16	8	8	8	8	8	0	0	0
Mg. FII N in 0.3 ml.	1.60	0.80	0.40	0.20	0.10	0.05	0.025	0.013	0.007

* Figures are reciprocal of highest dilution of euglobulin-yielding precipitate. (Serial twofold dilutions from 1:2 to 1:32.)

† Patients with rheumatoid arthritis.

the titer. These findings are similar to those reported by Pike, Sulkin and Coggeshall [29] for the serums of rheumatoid arthritic patients. Upon cold fractionation, FII-agglutinating activity was confined to the precipitate in all serums except that of one patient (G. L.), in whom only the supernate retained the agglutinating activity. The RAF in most of the "lupus" serums studied by Svartz and Schlossmann failed to precipitate when the serum was diluted in cold water, in contrast to that reported for the serums in persons with rheumatoid disease. However, the presence of this factor in the supernate, as discussed by Vaughan [7], may indicate a difference in solubility of agglutinating factor ascribable to serum proteins associated with

it rather than differences in the factor itself. HCl-euglobulin latex titers were positive in all patients, but slight or variable activity in the SSC and FII SC tests was of particular interest. (Table III.)

Bilirubin solutions in concentrations of 8 mg. per cent were made up in saline solution buffered at a pH of 8, with 0.9 ml. buffer and 0.1 ml. of serum from patients (H. B. and E. N.). For these two patients a 2 and 5 tube reduction of titer, respectively, occurred in comparison to controls lacking bilirubin.

Ultracentrifugation Studies. Specific agglutinating activity (Table V) was increased approximately five to 100 times by a single density gradient ultracentrifugation. Agglutinating activity was confined to dialysates of the bottom gel layer. Blood pigments were restricted to the top layer on visual inspection. This finding, together with an inhibitory effect of bilirubin on the positive reactions, makes it unlikely that the pigments have any significant role in production of the positive agglutinations. Except in the two serums of two patients (P. S. and C. W.) the protein content in the bottom gel was one-fourth to one-half 7S and the remainder 19S material. Inasmuch as the upper layers contain a major fraction of 7S material, absence of FII latex agglutinating factor in any except the bottom layer militates against its being a 7S component. A titer of 1:1280 was found in the serum bottom layer of one patient (C. W.) which contained no detectable

TABLE IV
AGGLUTINATION TITERS IN RELATION TO TEMPERATURE EFFECTS, SERUM FRACTIONATION, AND
DIFFERENCES OF SEROLOGIC METHOD

Patient	Whole Serum						Duration of Freezing (mo.)	HCl-Euglobu- lin Latex Titer (after freezing)	Cold Precipitable Globulin Precipitate	Whole Serum		
	Effect of Heating at 60°C. (min.)				Effect of Freezing					Super- nate	FuSC	SSC
	30	60	90	120	Be- fore	After						
A. S.	160	160	40	Negative	160	80	12	28
P. S.	80	80	Negative	Negative	80	80	2	28	80	Negative	112-Negative†	14-Negative
E. N.	80	40	Negative	Negative	80	80	12	...	40	Negative
G. L.	320	320	320	C*	320	320	12	14	Negative	320	896	14-Negative
A. Pr.	1280	320	80	Negative	1280	1280	2	28	320	Negative	3584	896
J. L.	640	640	320	Negative	640	640	4	28	1280	Negative	3584	14-Negative
L. M.‡	640	320	160	Negative	640	640	12	28	320	Negative	14336	...
H. B.‡	1280	320	160	Negative	1280	1280	12	28	160	Negative	7168	...

Note: Figures = reciprocal values.

* C = congealed.

† Considered negative because of incomplete agglutination at titer of 1:56.

‡ Patients with rheumatoid arthritis.

TABLE V
ULTRACENTRIFUGATION STUDIES

Patient	Disease	Serum Sample	Latex Titer		Concentration of Rapidly Sedimenting Material (mg./ml.)		Whole Serum		Bottom Fraction from Gradient Ultracentrifugation of Serum									
									Latex Titer		Analytical Ultracentrifugation							
			Observed		Specific*	19S	>19S	Observed	Specific	S _{20,w} ⁰ mg./ml.	Per cent of Total Protein	S _{20,w} ⁰ mg./ml.	Per cent of Total Protein	S _{20,w} ⁰ mg./ml.	Per cent of Total Protein	S _{20,w} ⁰ mg./ml.	Per cent of Total Protein	>19S
P. S.	Portal cirrhosis	A	1:80	1:80	0.8	3.00	None	1:30	23	6.9	86	19.3	14	0.48	14	19.3	14	None
A. S.	Portal cirrhosis	A	1:160	1:160	3.1	4.46	None	1:160	290	6.7	49	19.8	51	0.28	51	19.8	51	Trace
		A	1:160	1:160	3.1	5.50	0.90	1:160	81	6.9	52	20.0	40	0.80	40	20.0	40	0.16
H. J.	Portal cirrhosis	A	1:40	1:40	1.0	1.68	None	1:320
G. L.	Postnecrotic cirrhosis	A	1:640	1:640	8.5	1.94	None	1:80	400	6.6	70	20.1	30	0.06	30	20.1	30	None
A. P.	Thrombophlebitis	A	1:1280	1:1280	21.0	2.46	None	1:2560	940	6.4	64	18.4	36	0.97	36	18.4	36	None
J. L.	Pyelonephritis	B	1:1280	1:1280	18.0	3.54	None	1:640	690	7.1	71	19.9	29	0.27	29	19.9	29	None
		C	3.00	None	1:80	250	7.2	71	20.3	29	0.46	29	20.3	29	None
		D	1:640	2,000	6.8	74	20.2	26	0.06	26	20.2	26	None
C. W.	Rheumatoid arthritis	A	(FuSC titer 1:14000)	1:14000
		A	1:640	1:640	9.1	1.24	None	1:1280	12,000	Faint trace	...	19.4	100	0.11	100	19.4	100	None
H. B.	Rheumatoid arthritis	B	1:640	1:640	9.1	1.50	0.22	1:160	65	6.6	83	18.7	17	0.42	17	18.7	17	None
L. M.	Rheumatoid arthritis	A	1:640	1:640	9.8	1:160	250	7.0	51	19.5	49	0.32	49	19.5	49	None
		A	1:640	1:640	9.8	1:160	220	6.8	56	19.3	44	0.32	44	19.3	44	None
J. P.	Normal	A	Negative	Negative	...	3.26	None	6.9	74	19.1	26	0.34	26	19.1	26	None
R. P.	Normal	A	Negative	Negative	...	2.00	None	6.5	69	19.6	31	0.43	31	19.6	31	None
		A	Negative	Negative	None	6.8	63	20.0	37	0.45	37	20.0	37	None
B. B.	Normal	B	Negative	Negative	...	2.76	None	5.3	75	19.5	25	0.42	25	19.5	25	None
		B	Negative	Negative	6.9	78	19.3	22	0.36	22	19.3	22	None

* Reciprocal of latex titer/mg. protein/ml. starting solution.

7S material. Considering the insensitivity of ultracentrifugal methods to detect small amounts, 7S material may have been present in this layer. Small concentrations of 22S macroglobulins might have been present without detection in all of these low-titered serums. Traces of an S^{0}_{20w} peak of 37.5 and 28.4, were observed in two serums; however, small amounts of such rapidly sedimenting materials have been found occasionally under normal circumstances [23]. Ultraviolet spectral data (not presented) on the ratio of optical densities at 278 and 251 $m\mu$ /mg. nitrogen were within the range expected for plasma proteins containing tyrosine and phenylalanine.

COMMENTS

Tawil and Wahab [30] were the first to provide a substantial series of patients with hepatic disease and positive tests for RAF, although a number of sporadic cases previously were recorded [8]. To our knowledge, there have been no prior attempts to characterize the agglutinating factors of such serums. The RAF in the various serums tested here were similar to RAF of rheumatoid serums in respect to precipitin curves, stability at hot and freezing temperatures, and behavior of reactivity after various fractionation procedures. Kunkel observed a series of patients with sarcoidosis in whom the serum manifested a high titer of RAF. Not only was the agglutinating activity confined to the 19S fraction by density gradient ultracentrifugation, but a 22S component similar to that present in high-titered rheumatoid serums was detected in one patient [9]. Peltier and Christian [10] found the RAF of the serums of syphilitic persons in 19S fractions. Their precipitin curves of patients with syphilis using Cohn's fraction II as reactant resembled curves of patients with rheumatoid arthritis; these curves and those demonstrated in Figure 1 for hepatic disease also are alike [10,19]. Furthermore, separate absorption of Wassermann antibody and RAF from these serums failed to alter the tests for RAF and reagin, indicating the non-identity of these two factors [10].

Despite this characterization of agglutinating factors in six patients, there is the possibility of non-specific agglutinating phenomena causing positive tests for RAF in the remaining 18 patients. Positive reactions in low titers might result from differences in stabilizing factors,

activity of complement and presence of conglutinin [7]. Even in circumstances in which tests for RAF result from similar macroglobulins, it is unlikely that reactivity can be attributed to a single agent. Although the data are incomplete (Table IV), failure of positivity in FII-SC and SSC systems of certain serums suggests a lack of identity of RAF among them. Differences in reactivity of RAF depending upon the sensitizing globulin and agglutinable particle have been well catalogued [31,32]. Lospolluto, Lewis and Ziff [33] separated RAF by ion exchange chromatography into two distinct purified macroglobulins. Whereas both fractions reacted in the tanned sheep cell system, only one reacted to the SSC test [33]. The former but not the latter RAF fraction was detected in serums of patients with liver disease. Heimer *et al.* [34,35] absorbed RAF onto sensitized sheep red cell stroma. Supernates from their procedure contained at least three macroglobulins which were reactive in tanned FII-SC tests and were distinguishable from the macroglobulin eluted from the stroma. Inasmuch as most of the positive reactions in non-rheumatic diseases have been obtained with FII techniques, it may be conjectured that the macroglobulin adsorbed on the stroma of sheep cells is the more specific for rheumatoid arthritis.

Although the frequency of tests with positive results based on small numbers of patients may be misleading, it is likely that this incidence is higher in patients with specific diseases of the liver than with syphilis, sarcoidosis, malignancies, leukemia or other disorders thus far studied. The factors effecting this high rate of positive agglutination reactions in disease of the liver are unknown. Abnormalities of serum proteins reflected in the electrophoretic patterns, in the results of thymol turbidity and cephalin flocculation tests not only are the hallmark of hepatic disorders but frequently occur in rheumatoid serum [36]. Investigators have given considerable attention to the possibility that a liver derangement is involved in the pathogenesis of rheumatoid arthritis because of these serologic similarities and the frequent presence of "liver palms" [36]. The finding of like FII-agglutinating factors in hepatic diseases is consistent with this thesis but most evidence does not support it. The frequency of hepatic disease in patients with rheumatoid arthritis reported by Short *et al.* did not exceed the frequency of hepatic disease found in a control group [37].

No convincing evidence of significantly altered function of the liver has been noted [38] nor have any characteristic histologic lesions in the livers of patients with rheumatoid arthritis been found at postmortem examination [39,40,41]. Furthermore, in two publications, biopsy specimens of the liver in a total of fifty patients with rheumatoid arthritis revealed cirrhosis or hepatitis in only three [41,42]. Of interest in this connection is a group of patients reported by Bearn, Kunkel and Slater [43] with chronic hepatitis and polyarthritis which was indistinguishable in certain instances from rheumatoid arthritis. Tests for RAF were not reported but possibly there may be a relationship of the arthritis in this syndrome to classical rheumatoid arthritis.

Another consideration is that among the patients with disorders of the liver and positive FII-agglutinating serums the disease entity most commonly encountered has been viral hepatitis [8]. It must not be overlooked that among the group of patients diagnosed as having chronic hepatitis or cirrhosis there is the possibility of a viral carrier state [44,45]. However, a growing list of non-viral diseases such as essential hypertension, peptic ulcer and syphilis interdicts the suggestion of more than a limited relationship to viral agents [10,13].

Finally, the consideration that the FII-agglutinating factors produced in liver disease are antibodies warrants mention. The antigenic stimulus hypothetically includes the following: (1) a viral agent or other foreign organism; (2) an interaction product of invading organisms and host tissues; and (3) normal or altered host tissues not previously exposed to antibody-producing cells until the time of disease, according to Burnet's self-marker theory [46]. The principal arguments for the view that RAF may constitute antibodies are discussed in detail by Vaughan [32]. Evidence favoring this view derives from immunologic studies of RAF, teleological considerations, and the detection of other factors reactive with human tissues in serum of patients with different diseases [7]. Such autoreacting agents have been detected in thyroid disease [47,48], hemolytic diseases [49] and systemic lupus erythematosus [50]. Also, MacKay and Gajdusek [51] produced evidence for the development of complement-fixing antibodies to ground liver fractions from patients with chronic hepatitis. Three of these patients had postnecrotic cirrhosis, ascites and other evidence of advanced liver derangement follow-

ing acute viral hepatitis [51]. These patients had positive L.E. preparations, such as manifested by one patient (G. L.) in the present study. In addition to the lupus erythematosus factor, the serum of this patient contained complement-fixing antibody to nucleoprotein (titer 1:16), antibody to mouse liver nuclei, and FII-agglutinating factors detected by latex and sheep cell methods. At autopsy there were no gross or histologic signs of systemic lupus erythematosus. It should be emphasized that the presence of such autoreacting factors may bear only a distant relationship to those processes causing tissue damage, inasmuch as no demonstration of self-injury by these materials has been reported [7].

SUMMARY AND CONCLUSIONS

1. Fourteen of forty-three patients with a variety of hepatic diseases and ten of 164 patients with various chronic and acute inflammatory diseases revealed agglutinating serums in FII sheep cell or FII latex tests. The majority of patients with positive agglutinations and hepatic disease suffered from acute hepatitis or portal cirrhosis.

2. Characterization studies were made of FII-agglutinating factors in the serums of six of these patients with non-rheumatic disease. Fractionation procedures, precipitin curves on whole serum and euglobulin, and studies by density gradient ultracentrifugation failed to disclose any distinguishing features between the serums of patients with rheumatoid arthritis and those with non-rheumatic diseases.

3. The probability that the FII-agglutinating factors in these six patients are 19S macroglobulins of similar (although not necessarily identical) properties is discussed, and current views on the possible origin of FII-agglutinating macroglobulins in non-rheumatic diseases are elaborated.

Acknowledgment: We are indebted to Dr. Charles Christian for performance of the FII-SC and SSC tests, to Dr. Emil Taxay for the use of clinical data in one patient (P. S.), to Dr. Arthur Allen for review of pathologic material in a second patient (G. L.), to Dr. Howard Goodman and Dr. R. A. Malmgren at the National Institutes of Health for serologic studies in this patient.

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Reviews

Pulmonary Mechanics*

A Unified Analysis of the Relationship Between Pressure, Volume and Gasflow in the Lungs of Normal and Diseased Human Subjects

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FROM a mechanical point of view the lung consists of a large conglomerate of minute, expansile air spaces that ventilate to the atmosphere through a complex arborized airway. The air spaces and air passages contain fluid surfaces and tissue that possess quasi-elastic properties. For simplicity one may consider all of these elastic elements to act as a continuous three-dimensional elastic mesh ramifying throughout the entire lung parenchyma. During breathing the tension in the "mesh" increases during inspiration and decreases during expiration. Part of this mesh is inserted on the outer surface of the intrapulmonary airways and part on the inner surface of the visceral pleura. The significance of this for purposes of this paper is twofold. First, increased tension in the mesh inserted on the outer surface of the airways will dilate the associated air passages causing decreased frictional resistance to gas flow, and conversely, decreased tension will allow the airways to attenuate causing increased resistance to gas flow. Second, when the lung is at rest the tension in the mesh inserted on the inner surface of the visceral pleura is counterbalanced by a pressure drop across the pleural surface, the transpleural pressure.‡ Therefore, pressure acting on the outer surface of the visceral pleura, the intrapleural pressure, will be negative with respect to the subpleural air space pressure when there is no flow. Since

intrapleural pressure also acts on the outer surfaces of the extrapulmonary intrathoracic airways, the elastic mesh tension will also influence the diameter of these airways. Thus, the diameter of all the intrathoracic airways, both intrapulmonary and extrapulmonary, is in part determined by the degree of tension developed in the elastic mesh. Tension in the elastic mesh is related to the degree of lung inflation, hence one might predict that the gas flow along the airways will depend not only on the transpulmonary pressure§ but also on the degree of lung inflation. Recent studies do in fact indicate that this is the case and that the mechanical behavior of the lung may be rather uniquely and completely described by the simultaneous measurement of transpulmonary pressure, lung volume and respiratory flow [1,2].

In recent years considerable effort has been devoted to the study of the mechanical factors involved in respiration. Particular emphasis has been placed on measuring the rate at which the lung empties during a forced expiration, the compliance of the lung, the frictional resistance to gas flow into and out of the lung, and the work of breathing. Although extensive clinical experience has demonstrated the usefulness of many of these measurements in various cardiopulmonary disorders, their physiologic interpretations have perhaps been viewed from too narrow a perspective. It will be the purpose of this paper to

‡ The transpleural pressure is defined as the difference between the pressure in the subpleural air spaces and that acting on the outer surface of the visceral pleura.

§ Transpulmonary pressure is defined as the difference between the oral pressure and the pressure exerted on the visceral pleural surface of the lung.

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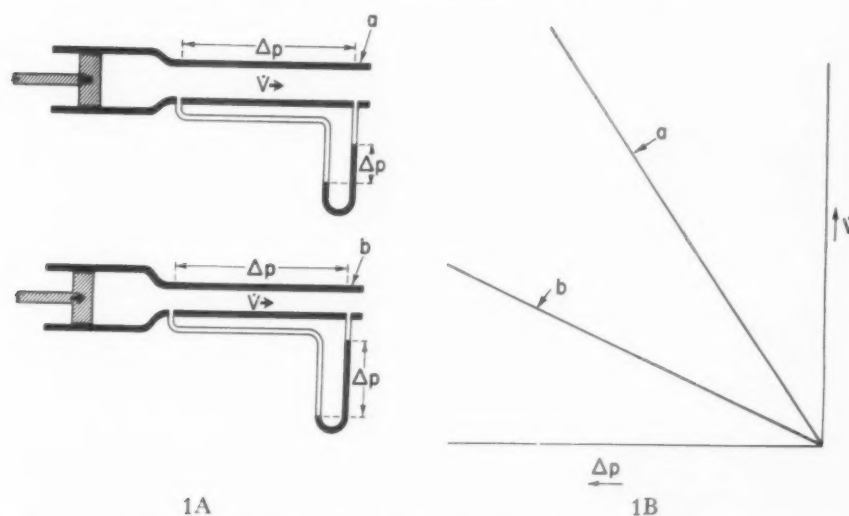


FIG. 1. A, models of uniform rigid tubes in which the relationship of pressure (Δp) to flow (\dot{V}) created by the motion of the piston may be studied. Tube, a, has a greater diameter than tube, b, B, graphs showing the relationship of pressure drop along the tube (Δp) to flow (\dot{V}) for the two tubes shown on the left. Arrows indicate the direction of increasing flow and pressure.

present a unified scheme relating transpulmonary pressure, flow and volume and also to integrate various common clinical observations and tests into this relationship.

THE INTERRELATIONSHIP OF TRANSPULMONARY PRESSURE, RESPIRATORY FLOW AND LUNG INFLATION IN A SIMPLE LUNG MODEL

As has been discussed, when the lung is at rest the pressure between the intrapleural surfaces, i.e., the intrapleural pressure, is always less than that in the subpleural air spaces by an amount necessary to counterbalance the tension in the elastic mesh. During breathing, however, these air spaces are being deformed. As with all tissues, the lung parenchyma offers a frictional resistance to changing deformation, sometimes called tissue viscous resistance. Thus, during breathing an added pressure increment must be developed between the subpleural air spaces and the intrapleural surfaces to overcome this tissue frictional resistance. This increment would be negative during inspiration and positive during expiration tending to increase the negativity of the intrapleural pressure during inspiration and decrease it during expiration. *In vivo* studies designed to assess the relative importance of this pressure increment to overcome tissue friction have necessarily been crude and indirect and have given variable results. Current belief is, however, that tissue friction is relatively unimportant when compared to the frictional resistance to gas flow in the pulmonary airways [3].

Frictional resistance to gas flow along the pulmonary airways is relatively large under certain circumstances and is intimately associated with the pathologic physiology of some cardio-pulmonary disorders. Although a comprehensive discussion of pulmonary aerodynamics exceeds the scope of this report, a brief simplified review of the physics governing flow through a simple elastic tube may be useful in thinking about the pressure-flow-volume relationships that follow.

Let us first consider flow through a uniform rigid tube, a, shown in Figure 1A. As the piston is advanced from left to right, a pressure gradient is developed along the tube resulting in a pressure difference, Δp , between the ends of the tube causing a flow, \dot{V} , that is proportional to the magnitude of this pressure difference. A plot of Δp and its corresponding flow for this tube appears in Figure 1B as curve a. If a similar tube having a smaller diameter, tube b in Figure 1A, is studied, it will be found to have a smaller flow for a given pressure drop, as shown by curve b in Figure 1B. The second tube is said to have greater resistance to flow than the first tube. It is customary to define flow "resistance" (R) as the ratio of the airway pressure drop to the resulting

flow, or $R = \frac{\Delta p}{\dot{V}}$. In this case the resistance (R)

is the reciprocal of the slope of the pressure versus flow (P-F) curves in Figure 1B. Clearly, the resistance of a tube can be constant only if the P-F relationship is a straight line.

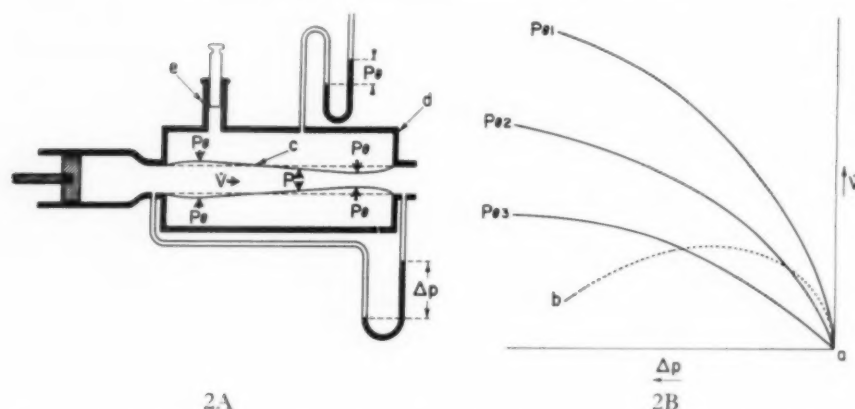


FIG. 2. A, model of an elastic tube "c" enclosed in a pressure chamber "d" in which the pressure ($P\theta$) may be varied by syringe "e." The difference between the chamber pressure $P\theta$ and the intraluminal pressure P is the transmural pressure which determines the shape of the tube. The dashed line indicates the resting shape of the tube, i.e., then $P = P\theta$ everywhere. B, the relationship of the flow (\dot{V}) to the pressure drop (Δp) in the elastic tube for various chamber pressures ($P\theta$). The dotted curve a-b is a hypothetical pressure versus flow curve for the tube when a functional relationship between $P\theta$ and Δp is imposed on the system.

Consider now the elastic tube, c, in Figure 2A which passes through the closed pressure chamber, d. The diameter at any point in this tube is related to the difference between the pressure acting on the inner surface of the tube (P) and the pressure, acting on the outer surface of the tube ($P\theta$). The pressure difference, $P - P\theta$, is defined as the transmural pressure. The magnitude of $P\theta$ may be varied by moving the syringe, e. When $P\theta = P$, the tube will be at its resting diameter. When $P\theta$ is greater than P , the diameter of the tube will be smaller than the resting diameter; when $P\theta$ is smaller than P , the diameter will be greater. Therefore, the diameter of the tube will tend to conform to the distribution of transmural pressure along its length. As with the rigid tube there will be a progressive decrease in the intraluminal pressure, P , along the length of the elastic tube due to pressure losses from frictional resistance to gas flow. The elastic tube conforms to this distribution of transmural pressure by progressively narrowing downstream. Now, in contrast to the rigid uniform tube, a second pressure drop related to this narrowing is created, that due to the Bernoulli effect.

The Bernoulli effect is the drop in pressure that occurs along a stream associated with the convective acceleration of the flow. Assuming steady flow, the mass flow (the grams of gas flowing per second) entering the tube from the piston chamber must equal that leaving the tube. The particles in the wider upstream part of the tube must speed up as they go through the narrow downstream portion. That is, they must experi-

ence an increase in velocity, called a convective acceleration, as they approach the narrowing to satisfy the condition that the same number of gas particles leave the tube as enter it in a unit of time. According to Newton's second law, an unbalanced force must be exerted on these particles to produce this acceleration. In a continuous substance forces appear as stresses or pressures. Therefore, to accelerate the particles through the narrowing, the necessary unbalanced force is created by a further progressive decrease in pressure along the tube. This additional progressive drop will further increase the tendency of the tube to narrow.

The exact behavior of the system in Figure 2A will depend on a number of factors including the physical properties of the tube, e.g., its stiffness, the dimensions of the tube, and the physical properties of the gas such as its viscosity, the flow, and the transmural pressure. The family of solid curves in Figure 2B are plots of the pressure drop (Δp) between the ends of the tube versus the flow (\dot{V}) for three different chamber pressures, $P\theta_1$, $P\theta_2$ and $P\theta_3$. As can be seen, as $P\theta$ is increased from $P\theta_1$ to $P\theta_3$, a greater pressure drop is required to produce a given flow.*

* Under certain conditions this type of system will become unstable so that the flow will oscillate and is no longer related to pressure in the simple manner outlined in Figure 2B. Although the theoretical treatment of this problem exceeds the scope of this review, this behavior is mentioned only to point out that the mean resistance to flow under such circumstances will tend to be even greater.

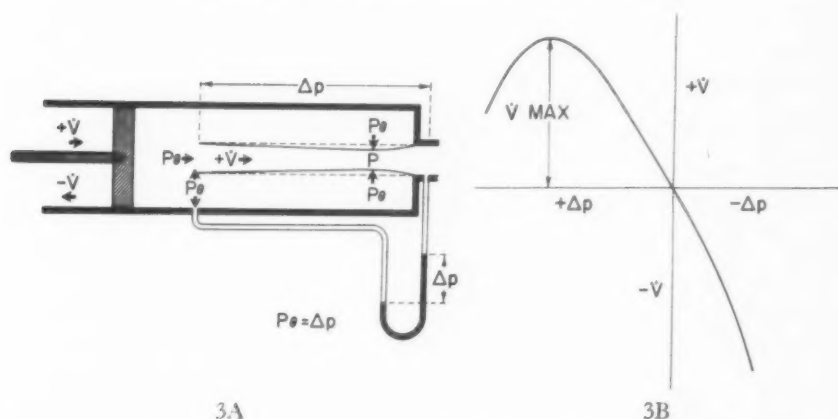


FIG. 3. A, model with one end of the elastic tube opening into the chamber. Motion of piston creates flow through the elastic tube. Piston is shown moving in expiratory direction producing progressive attenuation of the elastic tube from left to right. Although not shown, motion of the piston to the left would cause progressive dilatation of tube from left to right. B, the pressure flow relationship of the model in Figure 3A. Expiratory flow ($+\dot{V}$) is above the horizontal axis; inspiratory flow ($-\dot{V}$) below. Note that either $P\theta$ or Δp could have been plotted on the horizontal axis since in this model both are identical. \dot{V}_{max} is the maximum achievable expiratory flow.

Referring again to Figure 2A suppose now that instead of holding $P\theta$ constant, $P\theta$ is made to vary by moving the piston of syringe, *c*, in such a way that for every value of Δp there is a unique value of $P\theta$. In such a case the Δp versus \dot{V} relationship could be described by the dotted curve a-b in Figure 2B. When $P\theta$ and Δp are thus "tied" together by some fixed relationship, the system is no longer described by a family of curves but by a single curve since only one value of $P\theta$ can correspond to one value of Δp .

Consider now Figure 3A which represents a modification of the model in 2A. One end of the elastic tube opens directly into the chamber. In this situation the chamber pressure, $P\theta$, is equal to Δp since the pressures are generated in a common chamber. Thus, in the model in Figure 3A, $P\theta$ and Δp are tied together. Consequently only one flow down the elastic tube can exist for a given Δp . Therefore, the P-F relationship of this system is described by the single continuous curve shown in Figure 3B. As the piston is moved to the left a negative pressure is created in the chamber and air flows to the left through the tube into the chamber (inspiratory flow). Note that progressive increases in negative pressure within the chamber result in progressive increases in inspiratory flow. Furthermore, the transmural pressures developed in this situation will produce greater dilatation with greater inspiratory effort particularly in the portion of the tube to the right. This effect causes a fall in flow resistance and hence the

inspiratory curve bends toward the ordinate. The maximum inspiratory flow that may be achieved is limited only by the effort that can be exerted on the piston.

As the piston is moved to the right, a positive pressure is created in the chamber and air flows to the right from the chamber (expiratory flow). In this situation the transmural pressures that are developed tend to attenuate the tube. In contrast to the situation during inspiration, expiratory flow at first increases with pressure to a maximum value beyond which any further increases in chamber pressure will result in decreased flows.

The chamber pressure, $P\theta$, may be thought of as playing the following dual role: (1) supplying the pressure head for driving the flow through the tube and (2) of applying a dilative pressure during inspiration and a compressional pressure during expiration along the outer surface of the elastic tube. The point corresponding to the maximum of the expiratory portion of the P-F curve warrants special comment. It marks the point at which an increment increase in chamber pressure produces an increment in narrowing so that the resulting increase in flow resistance just balances the increase in driving pressure head with the result that there is no change in flow. Beyond this point additional increases in chamber pressure cause the tube to narrow further with the result that the effect of increased flow resistance exceeds that of increased driving pressure and flow falls.

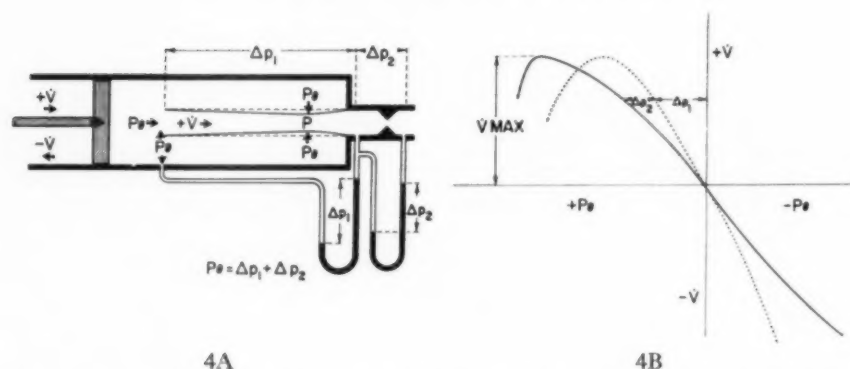


FIG. 4. A, the model of Figure 3A with added external resistance. The pressure drop across the external resistance is (Δp_2) and the pressure drop along the elastic tube (Δp_1). P_θ is now the sum of these pressure drops. B, the solid line represents the relationship between the total pressure drop (P_θ) to the flow (\dot{V}) for the model in Figure 4A. The dotted curve is the pressure drop (Δp_1) versus flow (\dot{V}). Note that this dotted curve is identical to the solid curve in Figure 3B indicating that the pressure flow relationship along the elastic tube is unaltered by the addition of external airway resistance. Since the elastic tube limits the maximum achievable expiratory flow, the maxima (\dot{V}_{max}) of the solid curve has the same flow value as the dotted curve, however, there is a pressure ordinate that is greater than that of the maxima of the dotted curve by an amount equal to the pressure drop along the external airway.

The flow value at which this maximum occurs is independent of the flow resistance of an external airway added to the outside of the chamber. Consider the system appearing in Figure 4A which is identical to the model in Figure 3 except for the addition of an external air passage creating an extrathoracic airway resistance. The P-F curve of this system appears in Figure 4B as the solid line. The pressure coordinates for every flow are now the sum of two pressure drops, the pressure drop along the elastic airway inside the chamber (Δp_1) and the pressure drop along the external airway (Δp_2). In contrast to the elastic tube, flow along the external resistance will be limited only by the amount of pressure, Δp_2 , that can be developed. As noted the P-F relationship of the elastic tube depends on its geometry which in turn depends among other things on its distribution of transmural pressure along its length. Since the added external resistance raises all pressures in the chamber and along the tube equally by an amount, Δp_2 , the values and distribution of the transmural pressures acting across the wall remain unaltered being determined only by the flow. The Δp_1 versus \dot{V} relationship of the elastic tube (the dotted curve in Figure 4B) remains unaltered by the addition of any Δp_2 . Thus, in this system it is still the behavior of the elastic tube, that determines the maximum achievable expiratory flow.

It is not possible to measure the separate pressure drops along the intrathoracic and extrathoracic airways in man routinely. P-F curves measured clinically, therefore, include both the pressure drop in the intrathoracic and the extrathoracic airways analogous to the situation in Figure 4. If the extrathoracic flow resistance is large and variable, it would not be surprising to find the P-F curves to be variable. As will be discussed later, this tends to be the case. On the other hand, from the foregoing data, one might expect the value of the maximum achievable expiratory flow to remain the same. More will be said about this important point.

The model in Figure 4A approaches an analogue of the human respiratory system. It would, however, represent a lung consisting only of elastic airways with no surrounding elastic mesh or lung parenchyma. Let us now consider the P-F relationships of the model in Figure 5A which is an analogue of the lung. The pulmonary elastic mesh and air spaces have been added to the model shown in Figure 4A. The elastic airway is divided into an intrapulmonary portion, I, and an extrapulmonary portion, E. The intrapulmonary part of the elastic airway has elastic tissue (symbolically shown as springs in Figure 5A) radiating from its outer surface that are held in tension by the transpleural pressure (P_L) thus, ($P_L = P_P - P_\theta$)

acting across the pleural surface. Both the diameter of this portion of the airway and the absolute value of the transpleural pressure will increase with increased tension in the springs and decrease with decreased tension. The tension in the springs in turn will vary with the volume of the air space containing the springs. Moreover, as discussed previously the transmural pressure created by P_L along E will tend to prevent collapse of the extrapulmonary intrathoracic part of the elastic airway.

Therefore, the geometry of the airway in the chamber depends not only on the distribution of transmural pressure related to the flow, as in the previous model, but also on the amount of tension in the fibers of the elastic mesh and the distribution of these elastic fibers on the outer surface of the intrapulmonary tube, I.* It follows that in this model the curve representing the P-F relationship will be different for different mesh tensions which in turn will depend on the volume of the mesh-containing air space. Thus there will be a family of P-F curves (Fig. 5B) each representing the P-F relationship at a different degree of inflation of air space or mesh tension.† The elastic mesh should be thought of as an integral part of the airway and thus for each degree of air space inflation one is simply looking at an airway with a different set of resting dimensions. Consequently, the P-F relationship, including the maximum expiratory flow point, will be different for each degree of lung inflation, as shown in Figure 5B. Each of these curves is an isovolume P-F curve.

As was the case in the previous model, the shapes of the isovolume P-F curves vary with upper airway resistance, but the flow value of the maximum on each curve remains independent of upper airway resistance, depending only on the flow characteristics and physical properties of the part of the system within the chamber. Since in this simplified analogue of the lung the properties of the intrathoracic system are assumed to

vary only with inflation,* the flow values of the maxima are uniquely related to the degree of inflation. If the maximal expiratory flows from the curves in Figure 5B are plotted against their corresponding volumes, the curve in Figure 5C which relates the maximum expiratory flow to air space or lung volume is obtained. This curve has been called the α F-V curve [2]. From the foregoing discussion it will be recalled that this curve should be unaffected by the flow resistance of the external airway and depend only on the physical properties and dimensions of the system contained in the chamber. The important physiologic implications of the α F-V curve will be discussed.

The term compliance has been mentioned. The relationship of the compliance curve to the isovolume P-F curves may be seen from the following: The air space pressure (P_p) is zero when the flow (\dot{V}) is zero. Therefore at zero flow in the model of Figure 5 the pressure drop between the chamber and the external mouth of the airway, P_θ , is the pressure (P_L) acting across the pleural surface to balance the elastic mesh tension, i.e. $P_L = P_p - P_\theta = -P_\theta$. As can be seen in Figure 5B this zero flow pressure difference on the isovolume P-F curves increases from P_{L1} to P_{L4} with increased inflation. If P_L were plotted against the inflation (V) represented by the corresponding P-F curve, a zero flow pressure-volume curve which is the compliance curve would be obtained.

Finally, it should be noted that the behavior of the lung model shown in Figure 5A can be completely described only if all three variables, flow (\dot{V}), pressure (P_θ), and volume (V), are measured simultaneously. Furthermore, if the inertial properties of the system may be ignored and if the system has "perfect" elastic properties, the behavior of the model will be uniquely determined by the three variables \dot{V} , P_θ , and V . For systems whose behavior is determined uniquely by these three variables it is common practice to express this behavior either as a family of curves representing the relationship between two of the variables at various arbitrary values of the third (as was done in Figure 5B) or as a single graph in a three dimensional space. This single graph would be a three dimensional surface having the coordinates of \dot{V} , P_θ , and V . As the piston in Figure 5A is moved back and forth, the

* The simple model in Figure 5A shows a progressive attenuation of the airway from left to right during expiration. This follows from the assumption of a uniform cylindrical tube. Obviously a more realistic model of the bronchial tree would consist of many branching parallel tubes with non uniform physical properties. In such a system the region of the greatest airway attenuation is not so simply determined [4].

† The curve shown in Figure 4B would represent the curve for zero mesh tension which if plotted to scale in Figure 5B would appear somewhere between the V_1 P-F curve and the $+P_\theta$, $-\dot{V}$ quadrant of the graph.

* This assumption is only approximately correct, as discussed elsewhere [2,4].

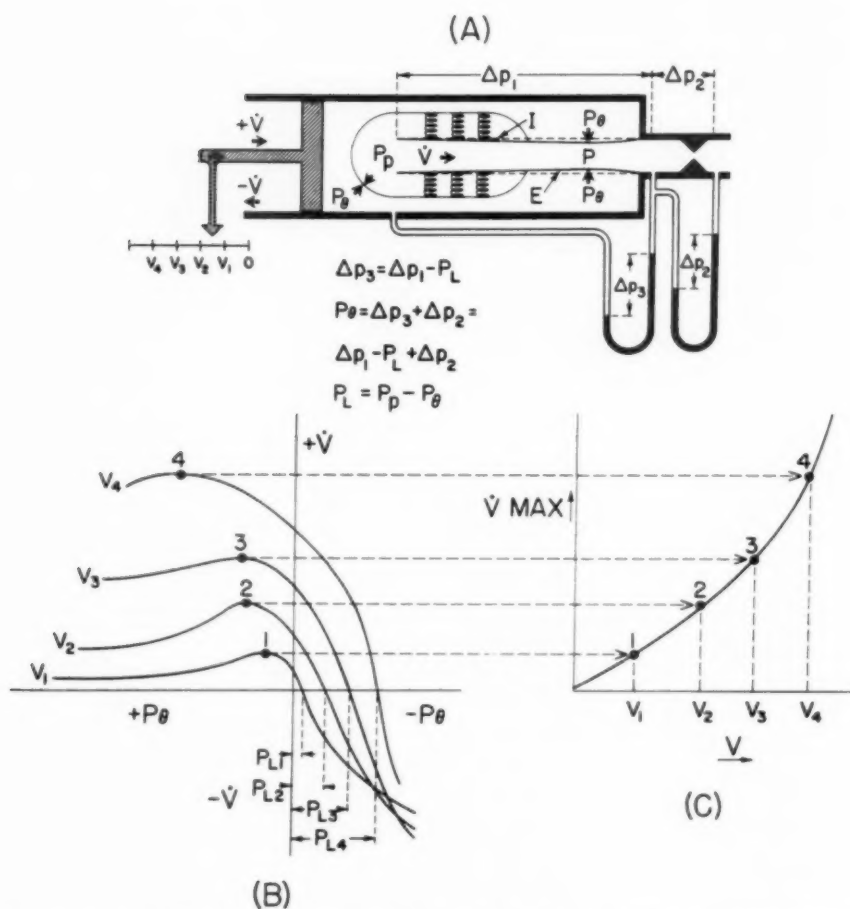


FIG. 5. A, a model the same as that shown in Figure 4A to which has been added an elastic "air space." The airway now consists of two parts; that inside the air space, I, and that external to the air space, E. The E portion of the elastic airway is subject to the transmural stress just as in the foregoing models. The I portion of the elastic tube is also partially supported by the tension in the elastic mesh of the air space which is shown diagrammatically by the springs connecting the outer surface of the elastic airway to the inner surface of the visceral pleura. A pressure difference (P_L) is created across this pleural surface to counterbalance the tension in the springs. As the piston is moved to the left, air flows into the elastic air space causing the springs to be stretched further, thus, increasing P_L . The position of the piston will be proportional to the volume of the elastic air space which is indicated by the scale and pointer on the piston rod. The pressure (P_p) in the elastic air space is the sum of the pressure drops along the entire airway ($\Delta p_1 + \Delta p_2$). Unlike the previous model the chamber pressure, P_θ now is the sum of the airway pressure drops, P_p , less the pressure P_L required to maintain inflation of the elastic air space. P_θ is now the analog of the transpulmonary pressure. B, graphs showing the relationship of chamber pressure P_θ (transpulmonary pressure) to flow along the airway (\dot{V}) for various degrees of air space inflation (V_1, V_2 , etc.). Note that at zero flow P_p equals zero and therefore P_L equals minus P_θ . A plot of increasing values of volume against the corresponding values of P_L would be the compliance curve for the model. Note that the expiratory ($+\dot{V}$) portions of the isovolume P_θ versus \dot{V} curves have maxima at 1, 2, 3 and 4. C, the α F-V curve of the model. The graph was constructed by plotting the flow values of the P-F curve maxima at 1, 2, 3 and 4 against the corresponding volumes V_1, V_2, V_3 and V_4 . Note that as the tension in the elastic mesh of the air space is increased by increased air space inflation higher maximal expiratory flows may be achieved.

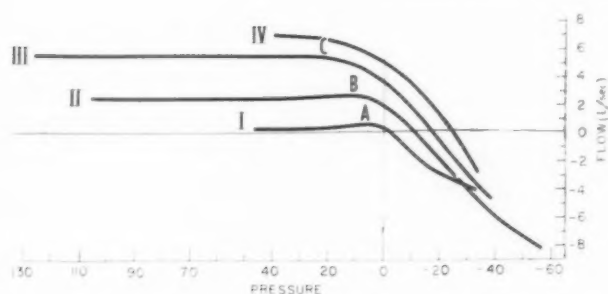


FIG. 6. Isovolum P-F curves from a normal subject. Curves I, II, III, and IV were measured at 0.5, 1.5, 2.5 and 4 L. above the maximum expiratory point, respectively. Vital capacity was 4.5 L. Note that the expiratory pressure flow curves, I, II and III have maxima at A, B, and C respectively.

instantaneous values of \dot{V} , $P\theta$, and V would form paths on this surface.

THE INTERRELATIONSHIP OF TRANSPULMONARY PRESSURE, RESPIRATORY FLOW AND LUNG INFLATION IN MAN

A method has been developed for obtaining satisfactory isovolume P-F curves in man [2]. The method consists of simultaneously and continuously measuring the intrathoracic pressure ($P\theta$ of the model) by the intraesophageal balloon technic, the respiratory flow by an appropriate flowmeter, and the degree of lung inflation by a recording spirometer. By choosing only pressure and flow points that correspond to a certain lung volume one may plot an isovolume P-F curve for that particular degree of lung inflation. Then, by choosing a different volume, one can plot another isovolume P-F curve. This procedure may be repeated until one has explored the P-F relationships over all lung volumes of interest. Relatively simple electronic technics may be employed which greatly reduce the labor involved in this method.

Using the aforementioned approach it has been shown that a relatively unique functional relationship exists between transpulmonary pressure, volumetric gas flow and degree of lung inflation in human subjects [1,2]. In Figure 6 the rate of gas flow has been plotted against transpulmonary pressure at four different degrees of lung inflation in a normal person. For example, the isovolume P-F curve III shows the relation between flow and pressure when the lung in this subject was at a volume of 2.5 L. above the residual volume. It should be noted that curves I, II, and III, which were measured at different

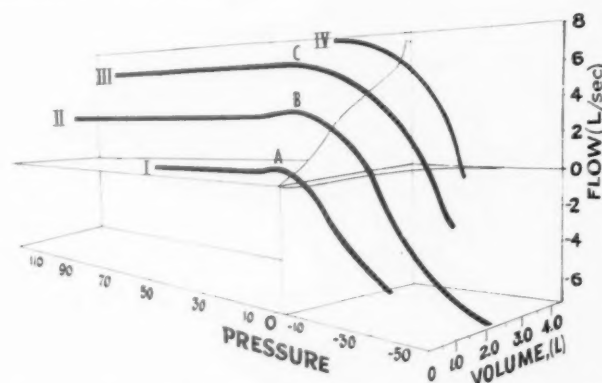


FIG. 7. The isovolum P-F curves of Figure 6 placed on a three-dimensional coordinate system. Flow in liters per second, volume in liters above residual volume, pressure in centimeters of water.

volumes over approximately the lower half of the vital capacity, have expiratory P-F maxima; that is to say, expiratory flow increases with increasing pressure to a maximum (points A, B and C, respectively) beyond which further increases in pressure cause a decrease in the rate of expiratory flow. Attention is drawn to the similarity of these curves from the complex pulmonary airway system to those obtained in the simple model of Figure 5. Maxima were not seen on P-F curves measured high in the vital capacity such as curve IV. Available evidence suggests that, if the subject was able to create sufficient intrathoracic pressure, P-F curve maxima could also be achieved even at the highest degrees of lung inflation. Inspiratory P-F curves do not have maxima for the reasons that were discussed in connection with Figure 3.

Since each isovolume P-F curve relates three variables, i.e., pressure to flow at a given volume, it is possible to represent this relationship in a three-dimensional coordinate system as has been done in Figure 7. Here the volume coordinate is plotted perpendicular to the plane of the paper with zero volume corresponding to the maximum expiratory point. The residual volume would then extend toward the reader in the negative volume direction. Each P-F curve in Figure 7 has simply been offset onto the volume axis to a position corresponding to the degree of lung inflation at which it was measured.

The ventilation of the lung could be described most completely by a great number of these isovolume P-F curves, all measured at different degrees of inflation. If many such curves were measured in a given subject and plotted in the manner shown in Figure 7, it is apparent that a

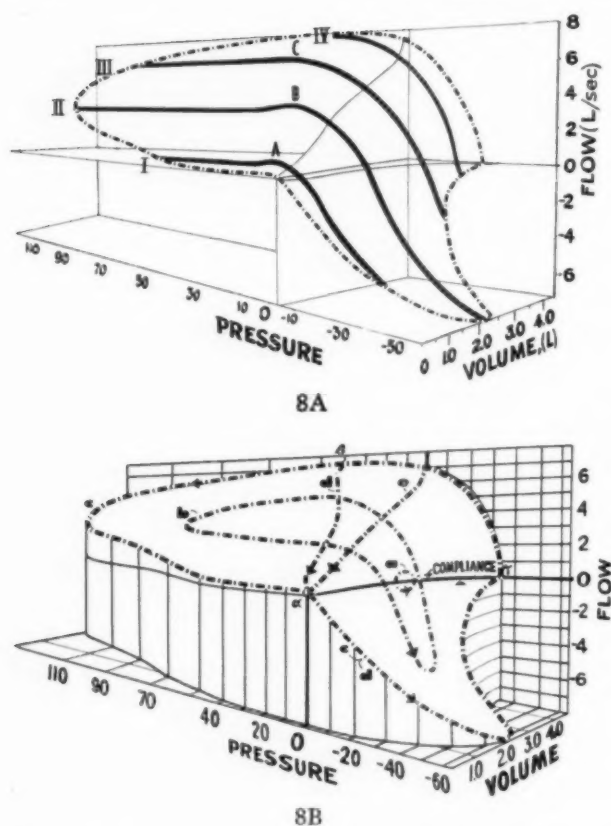


FIG. 8. A, a hypothetical three-dimensional surface outlined by the broken line that could theoretically be constructed from an infinite number of different isovolume P-F curves plotted as in Figure 7. B, the continuous three-dimensional surface of Figure 8A upon which paths of five different respiratory maneuvers have been plotted. The arrow heads indicate the direction of travel on these paths during each respiratory maneuver. a = tidal breath; b = MBC breath; c = maximum effort vital capacity breath; d = maximum flow vital capacity breath; e = free collapse curve. The intersection of the surface and the O flow plane is the compliance curve. α and γ are the terminal points of this curve. β is the point at which the paths of the maximum effort vital capacity and maximum flow vital capacity diverge.

continuous three-dimensional surface of the type shown in Figure 8A could be constructed. This surface would describe the simultaneous relationship between pressure* and flow at every volume point in this subject's vital capacity. The shape of the surface may vary somewhat from moment to moment for two reasons. First, the

* Although the pressure used in this construction is the transpulmonary pressure, an analogous surface could be constructed by using intra-alveolar pressure, as might be obtained from a body plethysmograph [5]. This surface would reflect the purely aerodynamic behavior of the lung ignoring the tissue frictional and elastic behavior and might be particularly useful in studying the problems of airway flow resistance.

physical properties of the lung itself, e.g., its elastic properties, vary somewhat depending on many factors which are not fully understood. Second, as was discussed in connection with Figure 4, the shape of the P-F curves can change with variations in upper airway resistance even though the physical properties of the lung itself might not change.

In spite of these limitations the three-dimensional surface concept has very real conceptual value in analyzing the complex mechanical events of pulmonary ventilation. This unified concept has proved quite useful both as a teaching device and as a framework for evaluating certain clinical observations as well as many of the methods of quantifying ventilatory mechanics presently used. From this concept has evolved an essentially unexplored aspect of ventilation, namely the α F-V curve previously mentioned in connection with Figure 5C. The details of obtaining this curve as well as certain of its theoretical aspects, are reported elsewhere [2,4].

With the foregoing background the clinical significance of the pressure-flow-volume relationship using the three-dimensional surface will now be examined. Any respiratory maneuver may be represented by a path over this surface. The paths of five breaths of different effort are shown in Figure 8B. Paths a, b, c, d and e represent a tidal, a maximum breathing capacity (MBC), a maximum effort vital capacity (MEVC), and a maximum flow vital capacity (MFVC) breath, respectively, as well as a free collapse curve (Curve e). A MEVC is a vital capacity maneuver in which maximal effort is applied throughout both inspiration and expiration. The usual forced expiratory vital capacity (FEVC) is comparable to the expiratory portion of the MEVC. The MFVC differs from the MEVC only in that the effort during expiration is controlled so that the flow corresponds to the P-F curve maxima. Hence, in this maneuver less than maximal effort is applied over most of the expiratory vital capacity. The free collapse curve is the path followed when the lung is allowed to collapse in such a manner that the transpulmonary pressure is kept at zero [6]. This is a special type of breath which has only an expiratory path and therefore does not form a closed path over the surface.

Thus, during the process of breathing, since volume is changing continuously, a person may be thought of as moving from one isovolume

P-F curve to another on this three-dimensional structure. The resulting rate of gas flow at any moment will be determined by the pressure applied and the volume at which the effort is made. Thus at a given instant any respiratory maneuver will have unique values of pressure, flow and volume. These three-dimensional paths formed by the breaths can be studied most simply by examining their projections as well as that of the surface onto the three coordinate planes. These projections might be readily visualized if the surface were made transparent, the three-dimensional paths made opaque, and the line of sight carefully oriented perpendicularly to the particular coordinate plane of interest. These projections would be identical to the loops obtained by recording any two of the three variables simultaneously during the particular breathing maneuver on the X and Y axes of the oscilloscope.

THE PRESSURE-VOLUME PLANE

The surface in Figure 8 has been redrawn at the top of Figure 9. In addition, contour lines representing constant flow have been drawn on this surface. When this surface is viewed along the line of sight indicated by arrow 1, the projections of the paths and contour lines onto the P-V plane are seen in the lower portion of Figure 9. The projections of the contour lines represent constant flow isopleths.

The zero flow isopleth or compliance curve* has particular significance in that it reflects indirectly the properties of the elastic mesh of the lung. The shape of this curve is controlled not only by the behavior of the elastic elements of this mesh (e.g. the elastic and collagen tissue, the surface tension of the fluid lining the air spaces, and the elastic behavior of the pulmonary vasculature) but also by the effectiveness with which these elements can exert traction on the inner surface of the visceral pleura. In the case of uneven ventilation of the lung, regions ventilating poorly will tend to "splint" the mesh locally, altering the tension that can be applied to the inner surface of the pleura by the elastic elements. Furthermore, in situations where there has been destruction of some of the elastic elements of the mesh there will be fewer elements

* The simplest method of obtaining the compliance curve is to measure the transpulmonary pressure at zero flow when the lung is at various degrees of inflation [7].

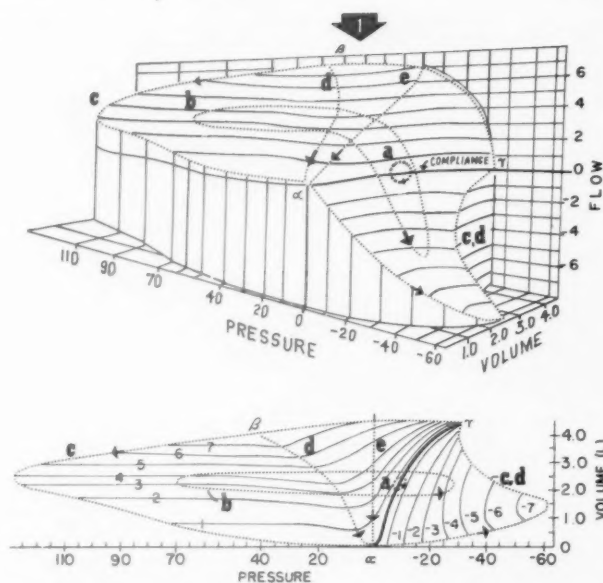


FIG. 9. The surface and respiratory paths of Figure 8B redrawn with constant flow contour lines appears at the top of this figure. When this surface is viewed along the line of sight of arrow 1, the pressure-volume projection of the surface will be seen as the diagram in the lower part of this figure. The pressure is in centimeters of water. The numbers on the constant flow lines are liters per second. Inspiration to the right and expiration to the left of the α - γ curve (compliance curve).

exerting tension on the inner visceral pleural surface.

The compliance curve will not be a unique curve to the extent that the elastic elements comprising the mesh are imperfect elastic bodies and to the extent that uneven ventilation exists [8,9]. Nevertheless, for simplicity it is possible conceptually to consider the compliance curve of the lung as being represented by a single curve at any given moment.

The shape of the compliance relationship is curvilinear, being approximately a straight line in the region of the functional residual capacity. In general only the slope of this relatively straight part of the curve has been used to characterize the elastic properties of the lung. The slope is the change in volume (ΔV) per unit change in transpulmonary pressure (ΔP). This ratio is defined as the "compliance" of the lung,† its reciprocal the "elastance." Although these terms are usually only applied to the straight part of the curve, the notion of compliance can be applied more generally to the entire curve by

† In the case of uneven ventilation where insufficient time is allowed for the air space pressure to equalize throughout the lung, the slope of the zero flow pressure-volume isopleth is called the "effective compliance" [9].

considering the slope of a tangent to the curve at any point of interest. Since this curve is not a straight line, compliance will be a function of the volume, i.e., it may vary at every point on the curve usually becoming smaller with increasing lung inflation.

The slope of the compliance curve can be shown to be related to the problem of ventilation distribution and thus the measurement of compliance is significant in this regard. Furthermore, the absolute value of P_L along the entire curve is of significance since, as was discussed in connection with Figure 5, it in part determines the resistance to flow in the airways with resistance becoming less as P_L increases [10]. Thus, the conventional method of characterizing the compliance curve of the lung by the use of one constant, the mean slope or compliance in the tidal volume range, has certain limitations. It gives no information as to how compliance varies over the entire range of volume or as to the absolute value of P_L at any point on the curve.

The remaining constant flow isopleths in Figure 9 are now examined. Those to the right of the compliance curve are inspiratory flow isopleths and those to the left are expiratory flow isopleths. The inspiratory isopleths indicate that progressive decreases in pressure at any volume will produce progressive increases in inspiratory flow. In contrast to this, the expiratory flow isopleths over the lower part of the vital capacity indicate that at a given volume there are two pressures that correspond to a given flow. This reflects the characteristic shape of the expiratory portion of the isovolume P-F curves seen in Figures 6 through 8.

The area enclosed by each of the loops representing the breaths of varying effort is proportional to the amount of physical work done on the lung to overcome the frictional resistance of the gas flow and tissue. Note that during the tidal breath, a, the area on the right of the compliance curve is about equal to that on the left indicating that about as much mechanical energy is expended in the lung during inspiration as during expiration. This is not true of the MBC, b, or MEVC breath, c, where much more energy is dissipated during expiration. Note that the loop of the MEVC breath forms the perimeter of the entire diagram since it represents a maximal inspiratory and expiratory effort over the entire vital capacity. Notice also that the loop for the MFVC, d, is the same as that for the MEVC, c, throughout the inspira-

tory phase and during the part of the expiratory phase corresponding to the upper part of the vital capacity in which P-F curve maxima are not achieved. Thus the MFVC depends on maximum effort over this part of the path (from α to γ to β). At the point labelled β the loop of the MFVC diverges from that of the MEVC to follow a path (β to α) that is the locus of the pressure and volume coordinates of the P-F curve maxima. Since the pressures necessary for maximum flow in the β to α region are in general far less than those associated with the MEVC, there is far less energy expenditure during the performance of the MFVC. The free collapse, e, does not form a loop but simply follows the zero pressure coordinate.

If the extremes of negative and positive intrathoracic pressure that could be developed statically at every degree of lung inflation were measured, a maximal pulmonary pressure versus volume loop could be constructed [11]. It would be of interest to study the relationship of this static loop to the P-V loop of the MEVC in Figure 9. Recent studies suggest that the relationship between the effort of the chest and the resulting intrathoracic pressure may be an interesting area in which to explore the complicated problems of ventilatory control and dyspnea [12,13].

THE PRESSURE-FLOW PLANE

Consider now the projection of the three-dimensional surface with its paths on the pressure-flow (P-F) plane in Figure 10. This projection would be seen if the surface in the upper part of the figure were viewed along the line of sight of arrow 2 as shown. In this case the constant volume isopleths are the isovolume P-F curves.

It is possible to obtain the projection of these paths onto the P-F plane in human subjects by recording the loops formed on an oscilloscope face when respiratory flow and transpulmonary pressure are recorded simultaneously on the X and Y axes. Although the loop of the MEVC, c, determines the perimeter of the expiratory portion of the projection, it does not necessarily form the outer boundary of the inspiratory portion.*

* The precise contour of the inspiratory limbs of the isovolume P-F curves has not been well studied. As can be seen, low in the vital capacity maximal inspiratory effort appears not to correspond exactly to the maximal achievable flow at the same pressure were the subject at a somewhat higher volume.

As on the P-V plane the loop of the MFVC, d, separates from the MEVC, c, loop at the β point and travels far short of the positive pressures seen with the MEVC until their paths again converge at α . The pressure at which flow and pressure dissociate during maximally forced expiratory efforts has been recently studied [14]. High in the vital capacity this point of dissociation would depend on the rapidity with which the effort was developed. Lower in the vital capacity at volumes corresponding to the β to α portion of the MFVC this point should approximate the maxima of the isovolume P-F curves. Preliminary observations support this conclusion [15].

The reciprocal of the slope of a line drawn from the zero flow point on an isovolume P-F curve to any flow point on the same P-F curve is a measure of the frictional airway and tissue resistance of the lung at that flow and volume. As has been discussed, tissue frictional resistance plays a relatively minor role in determining the shape of the isovolume P-F curves. In emphysema there is an increased resistance to the flow of respired gas. Although there is some increase in inspiratory flow resistance, the greatest increase is encountered during expiration [1,16]. Hence the ability to measure small increases in expiratory flow resistance should be quite valuable in detecting early disease of the bronchial tree; however, certain problems arise in the measurement and interpretation of expiratory flow resistance data.

Most pulmonary disorders of physiologic interest occur in the airways and parenchyma below the larynx. All of the commonly used methods of measuring resistance yield the sum of both upper and lower airway resistance. Upper airway resistance is roughly half the over-all resistance of the normal respiratory tree during quiet breathing [17]. In addition, it may change unpredictably from moment to moment due to variations in attitude of the mouthpiece, tongue, teeth, glottis, etc. Random variations of this type may at times mask significant changes in lower airway resistance.

It has been shown that expiratory resistance measurements are also dependent upon volume [1,2,16,18]. This can be seen from the shape of the isovolume P-F curves in Figure 10 which bend more rapidly as the degree of lung inflation decreases. Therefore, at a given flow, the flow resistance varies inversely with the degree of lung inflation. It is obvious that the lung volume at

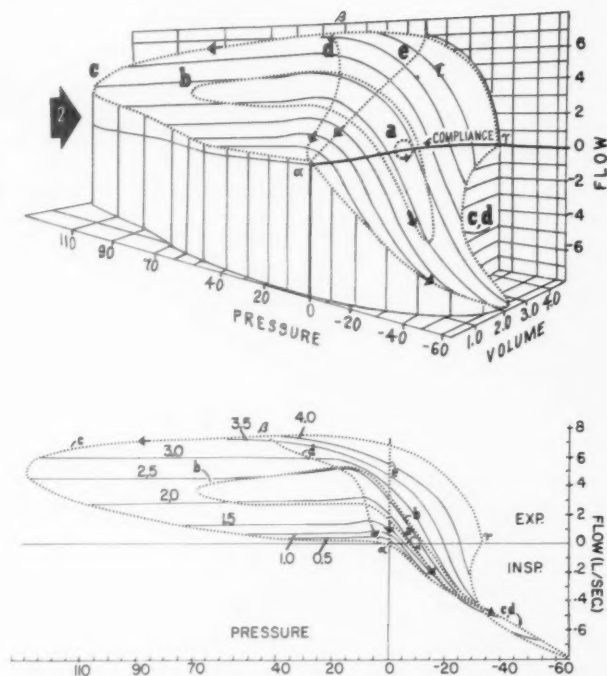


FIG. 10. The surface and respiratory paths of Figure 8B redrawn with constant volume contour lines (the isovolume P-F curves) appears in the upper portion of this figure. When this surface is viewed along the line of sight of arrow 2 the pressure-flow projection of the surface may be seen as the diagram in the lower part of this figure. Pressure is in cm H₂O. The numbers on the constant volume lines represent liters of inflation above the maximum expiratory point.

which resistance measurements are made is quite important and must be accurately controlled if one is to attempt to draw any inferences from these measurements about the function of the airway.

Expiratory resistance measurements are also dependent upon effort. This is particularly true over the lower half of the vital capacity where the isovolume P-F curves are extremely non-linear. Greater effort produces greater airway pressure drop. Since the resulting flow does not increase proportionately and indeed may even decrease, the computed resistance will increase rapidly with effort. Attempts to circumvent this problem by the use of various "resistance coefficients" based on mathematical curve fitting techniques have been moderately successful provided respiratory effort is sufficiently restricted [19,20]. However, with excessive effort it would be predicted that these techniques would also be unsatisfactory, giving a value of resistance which, aside from being large, would have little meaning. Thus, if expiratory flow resistance data are to be useful as a sensitive

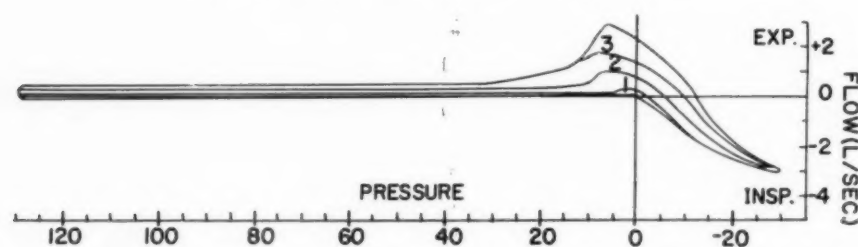


FIG. 11. The pressure-flow projection of a pressure-flow-volume surface constructed from data obtained from a subject with moderately severe pulmonary emphysema. Note that volume isopleths in this figure are 1 L. apart rather than $\frac{1}{2}$ L. apart as in the normal subject shown in Figure 10.

means of quantifying the functional behavior of the bronchial tree, careful attention must be paid to the facts that these measurements include the resistance of the upper airway, are dependent upon volume and effort.

The P-F plane projection of a three-dimensional surface obtained from a subject with moderately severe obstructive emphysema is shown in Figure 11. The general contour of the expiratory limbs of the P-F curves in emphysema are similar to those in normal subjects. On the other hand, it is interesting that the maxima occur at transpulmonary pressures often considerably less than those of normal subjects. With forced or labored breathing pressures may develop in emphysematous subjects exceeding those of the P-F curve maxima so that, under these circumstances, these patients will tend to breathe on the descending limbs of their P-F curves. The resulting expiratory flow rates will be below the maximal flow that they could achieve if they were to exert less pressure.

Furthermore, at a given pressure expiratory flow is very low at all lung volumes when compared to the normal flow. This accounts for the prolongation of the FEVC in these patients and is reflected in the associated decreased one-second vital capacity, MBC, maximum expiratory and mid-expiratory flow rates. Since significant increases in expiratory flow rates can only be achieved when breathing is performed high in the vital capacity, these persons tend to perform any rapid breathing well above their resting functional residual capacity. This accounts for the "trapping" or large increases in the functional residual capacity seen in these subjects during the performance of an MBC test.

There are certain clinical implications to be drawn from the isovolume P-F curves of the emphysematous subject. These persons should be taught to avoid excessive effort during expiration since this only serves to increase the expendi-

ture of energy and does not produce increased flow. This point has been stressed by Dayman [27] and has empirically become one of the guiding principles in the teaching of breathing exercises to these patients. Furthermore, since there is no evidence that these patients have any significant weakness of their respiratory muscles, it is difficult to justify the use of breathing equipment that actively assists expiration in this disorder. The large transpulmonary pressures developed by such devices only serve to decrease ventilation further and, under certain circumstances, might actually damage the lung. The patient with severe emphysema has only two means by which he can significantly increase ventilation (1) by raising his FRC and (2) by increasing inspiratory flow, thus shortening the time of inspiration and allowing more time for expiration. Therapeutic respiratory equipment to be used in such patients should be designed in light of these considerations.

Increased stimulation to breathing in patients with emphysema, such as by anoxia or increased respired carbon dioxide concentrations regardless of cause, will increase the intrathoracic pressure swings which if sufficiently great may actually decrease ventilation. Increased production of carbon dioxide and increased oxygen demand may result leading to a vicious cycle that fits well with the common clinical observation that emphysematous patients can precipitously deteriorate with relatively minor respiratory insults.

Preliminary observations in this laboratory suggest that the emphysematous subject can more readily achieve maximal expiratory flow at any degree of lung inflation if he is breathing against an added external resistance. This fits with the observation that these persons frequently seem to benefit subjectively from expiring through narrowed glottis or pursed lips. One explanation for the beneficial effects of this

procedure could be as follows. It was shown earlier in this report that the flow at the maximum on the isovolume P-F curve of the lung model was essentially independent of extra-thoracic airway pressure drop but did depend on the pressure drop along the intrathoracic airways. This also appears to be the case in man (*vide infra*). Large transpulmonary pressure swings occur with dyspnea or exertion in severe emphysema. In such subjects most of the pressure drop is in the intrathoracic airways and is so large that the system may operate well out on the descending limbs of the isovolume P-F curves. If the patient purses his lips with the same large transpulmonary pressures, he can move a large portion of this pressure drop to his upper airway, i.e., across his lips. Consequently, the drop occurring along the intrathoracic airways will be decreased by an equivalent amount and the flow system will operate back nearer the P-F curve maxima. Expiratory flow and hence ventilation will be increased. Changes of transpulmonary pressure in response to added flow resistance have not been thoroughly studied. The general problem of the factors controlling intrathoracic pressure would seem a fruitful area for further investigation, not only as it applies to emphysema but also to the more general problem of dyspnea and ventilation control.

THE FLOW-VOLUME PLANE

The surface of Figure 8 has been redrawn at the top of Figure 12 with isopressure contour lines. If this surface were viewed along the line of sight of arrow 3, its projection on the flow-volume (F-V) plane would appear as the lower diagram in Figure 12. Note that isopleths to the left of the β to α line on the surface have been omitted on the projection for simplicity. The pressure values of the four expiratory pressure isopleths that intersect the β to α line represent the pressures corresponding to the P-F curve maxima at the flows and volumes of intersection.

It is possible to obtain F-V loops in human subjects by placing the flow signal on the Y axis of an oscilloscope and the volume signal on the X axis. The F-V diagram would then be obtained by photographing the superimposed loops of the breaths of varying effort.

In contrast to the preceding P-V and P-F diagrams, the entire perimeter of the F-V diagram is the MFVC loop, d. As was also seen in the previous two diagrams, the MFVC and MEVC form loops that are identical over the

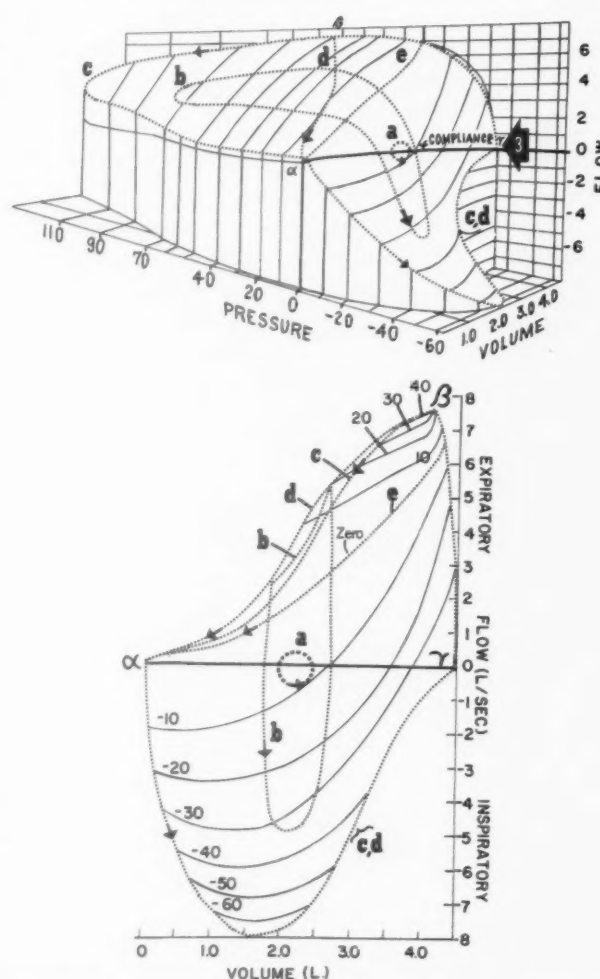


FIG. 12. The surface and respiratory paths of Figure 8B are redrawn in the upper portion of this figure with constant pressure contour lines. When this surface is viewed along the line of sight of arrow 3 the projection on the flow-volume plane of this surface would appear as the large diagram in the lower part of this figure. Note that isopleths of contour lines extending beyond the α - β line have been omitted for simplicity. The numbers on the constant pressure lines are in cm of H_2O .

inspiratory and early expiratory portions of their courses, i.e., the α to γ to β portion of the perimeter. This portion corresponds to the maximal effort of the subject. Since the isovolume P-F curves begin having maxima at β , the MFVC loop, as would be predicted, forms the outermost boundary of the part of the diagram between β and α . The MEVC loop, c, follows the outer rim of the three-dimensional surface which in the β to α region corresponds to lower flows. Thus, the F-V projection of the MEVC loop dips below the MFVC loop in this region. The MBC loop, b, in this person also dips below the MFVC loop touching it only at the points where the MBC effort momentarily

corresponds to the MFVC loop. This reflects the fact that during most of the MBC effort pressures in excess of those at the maxima were exerted.

The free collapse curve, *e*, corresponds to the zero pressure isopleth throughout expiration since it represents the flow that results when the frictional resistance of the lung tissue and airways is just balanced by the elastic mesh tension. Therefore, the transpulmonary pressure is zero throughout the entire maneuver. The F-V projection of this maneuver falls consistently below the MF loop since the P-F curve maxima always occurred at a moderately positive intrathoracic pressure.

It is seldom possible to obtain one single vital capacity effort that describes the MFVC loop. It is almost always possible to obtain the expiratory portion of this curve by having a subject perform a maximal inspiratory effort followed by a series of expiratory vital capacity breaths of varying effort [2].

It should be pointed out that in situations where the transpulmonary pressure is changing rapidly such as in cough [10,21] and MBC-type breathing the flow may momentarily exceed the β to α portion of the MFVC curve. Reasons for this are discussed elsewhere [2,4].

In the theoretical discussion of the lung model it was noted that the expiratory flow occurring at the maximum of an isovolume P-F curve depended only on the physical properties of the intrathoracic pulmonary system and, therefore, should be relatively invariant despite considerable variations in upper airway resistance. This has been experimentally confirmed [2]. Thus, over the range of lung volumes where the P-F curves have maxima, i.e., the β to α part, the plot of the maximum achievable expiratory flow against the degree of lung inflation is a relatively reproducible curve. The β to α portion of the MFVC has been termed the α F-V curve and has two important implications. First, with the exception noted in the previous paragraph, this relationship represents a relatively rigid mechanical limitation imposed on maximal expiratory flow for which no amount of added energy can compensate. Second, unlike many other ventilatory measurements which depend on maximal effort this relationship will be reproducible to the extent that the properties of the intrathoracic pulmonary system remain constant. The α F-V curve in normal subjects has been found to be quite different from that in

subjects with cardiopulmonary disease. Therefore, a rather detailed consideration of the possible clinical significance of this curve and its role in evaluating many of the common tests of ventilatory mechanics will be presented.

Many of the most useful indices of ventilatory mechanics are based on analyses of either flow or volume as a function of time.* The most common tests are based on various analyses of either the FEVC, which corresponds to the expiratory portion of the MEVC, or other related expiratory maneuvers. In Figure 12 it was seen that when this normal subject performed a MEVC, his curve on the expiratory part of the F-V diagram fell slightly below the MFVC curve over the β to α region.

The separation of the MFVC and the MEVC will depend on the effort exerted by the subject during the latter procedure. Thus, the FEVC test is effort-dependent over its entire course. Since over the γ to β portion of the F-V diagram P-F curve maxima are probably unattainable, it follows that maximal flows in this region of the vital capacity are extremely dependent upon effort. Thus, a potentially large degree of variability would be predicted for tests that quantify this portion of the FEVC, such as peak expiratory flow rates, the maximal expiratory flow (MEF) test [22], and tests measuring the volumes expired in the first 0.5 to 1.0 second. Although some studies tend to confirm this prediction [15], it is interesting that in practice these tests are reported by many to be useful and reasonably reproducible [22,23,24].

As previously mentioned over the lower portion of the vital capacity the FEVC curve in normal subjects corresponds rather closely to the α F-V curve. The α F-V curve is reproducible and is dependent upon effort only to the extent that sufficient transpulmonary pressure must be created to achieve the P-F curve maxima. Thus, it should follow that tests quantifying approximately the lower half of the FEVC should also be fairly reproducible. This has been found to be the case with the maximal mid-expiratory flow test (MMF) which is the mean flow rate occurring over the mid-portion of the FEVC even though this test includes a small portion

* Since flow equals dv/dt , it is simple to compute the time course of either flow or volume of any loop in the F-V plane by the simple formula, $dt = \frac{dv}{F}$, where *F* is flow. Thus, the MFVC curve may be readily converted to a conventional spirographic tracing.

TABLE I
EFFECT OF TENFOLD INCREASE OF EXTERNAL AIRWAY RESISTANCE ON VENTILATORY TESTS IN
NORMAL SUBJECTS

Normal Subject	Vital Capacity (L.)		One Second Vital Capacity (%)		Maximum Expiratory Flow (L./sec.)		Maximum Mid-expiratory Flow (L./sec.)		$E_{(50-75)}^*$ (L./sec.)		Log Q_{max}^\dagger		K †	
	Control Values*	Added Resistance Values	Control Values	Added Resistance Values	Control Values	Added Resistance Values	Control Values	Added Resistance Values	Control Values	Added Resistance Values	Control Values	Added Resistance Values	Control Value	Added Resistance Values
1	5.0	5.1	90	55	7.5	2.9	7.0	3.2	6.7	3.3	7.9	8.0	1.7	1.7
2	3.5	3.5	88	84	4.3	3.5	3.4	3.3	2.9	3.0	5.0	4.8	1.4	1.4
3	5.0	4.9	77	64	6.9	3.5	3.6	3.1	2.7	2.7	4.9	4.2	1.1	1.0
4	5.0	5.0	75	61	5.3	3.0	3.4	3.0	2.4	2.6	3.4	3.7	0.8	0.9
5	4.8	4.8	74	58	8.5	3.2	4.3	2.7	3.0	2.5	5.0	4.8	1.1	1.1
6	4.6	4.6	79	64	5.4	3.0	3.7	3.1	3.0	2.8	4.0	4.0	1.0	1.1
7	4.9	4.9	86	63	6.9	3.0	4.7	3.6	3.8	3.5	6.1	6.4	1.4	1.4
8	3.4	3.3	75	68	4.0	2.6	2.4	2.1	1.8	1.8	2.8	2.8	1.0	1.0
Average per cent change after added resistance <2 per cent change			20 per cent decrease		49 per cent decrease		26 per cent decrease		16 per cent decrease		<2 per cent change		<2 per cent change	

* The mean flow over the lower 50 to 75 per cent of the vital capacity.

† The α F-V curve was quantified by the two constants, Log Q_{max} and K as described elsewhere [2].

of the effort-dependent segment [25]. It is interesting that Franklin [26] recently reported that measurement of the mean flow occurring between the lower 50 and 75 per cent of the FEVC (E_{50-75}) was more reproducible and less subject to performance errors than were either the MMF or the one-second timed fraction. This fits well with the α F-V concept and is supported by observations in our laboratory (*vide infra*).

It has been pointed out that the MBC test has many sources of variability [22]. A glance at the F-V loops makes it clear that the reproducibility of MBC test depends on the lung volume and the cyclic rate at which the test is performed, as well as the effort exerted by the subject, particularly during inspiration. In practice it appears that the subject does tend to control these variables since this test has proved to be quite useful clinically.

Since in contrast to the β to α portion of the MFVC, the γ to β portion is dependent upon effort, it would be predicted that tests quantifying the upper portion of the FEVC should be more sensitive to changes in upper airway

resistance than measurements of the lower portion of the FEVC. To test this postulate a group of normal subjects had FEVC and α F-V curves determined before and after the addition of an external airway resistance which increased the over-all resistance to flow some tenfold. This can be likened to resistance increases that might result from narrowing of the glottal aperture, partial occlusion of the airway with the tongue or pursing of the lips. Referring to Table I it can be seen that there was no significant change in the total vital capacity, but the volume of air expired in the first second fell in all subjects when the external resistance was added, the average decrease being 20 per cent. Similarly the MEF test showed an average fall of 49 per cent. The external resistance caused a marked decrease in the MMF of one normal subject (1) and an average fall of 26 per cent in the entire group. The E_{50-75} only decreased 16 per cent with most of the change occurring in subject 1. The α F-V curve showed essentially no change. Thus, in normal subjects the α F-V curve, as predicted, is relatively unaffected by a marked increase in upper airway resistance. The upper portion of

the FEVC is very sensitive to such changes while the lower part of the curve is much less affected.

As noted previously, the α F-V curve in a given person defines the upper limit of expiratory flow over much of the vital capacity. Since the mean expiratory flow occurring with resting tidal respiration is quite similar in normal subjects and in emphysematous subjects, it is apparent that the amount by which the emphysematous subject can increase his expiratory flow above resting needs is severely limited. In fact, preliminary studies [15] have indicated that severely emphysematous subjects at rest breathe very near, and occasionally at, their α F-V curve. The possible significance of this relationship to the problem of dyspnea and as an index of the severity of bronchopulmonary disease is being explored.

SUMMARY

A three-dimensional graphic representation of the mechanical aspects of pulmonary ventilation has been developed from experimental data obtained in man, in which transpulmonary pressure, respiratory flow and lung inflation have been uniquely related. The basic element of this representation is the isovolume pressure-flow curve. The behavior of a simple lung model is described to emphasize the general determinants of these isovolume pressure-flow curves. The broad inferences drawn from analysis of this model are applied to the pressure-flow-volume (P-F-V) relationship of the human lung.

The three-dimensional surface representing the P-F-V relationship has had certain conceptual value. The concept of the α F-V curve evolved from consideration of this surface. This curve has been studied in man and found to have certain unique characteristics that suggest that it may become a valuable clinical tool. The α F-V curve is quite reproducible, is only moderately dependent upon effort, is essentially unaffected by wide variations in upper airway resistance, is determined by the physical properties and dimensions of the intrathoracic pulmonary system, is greatly altered in emphysematous subjects and is relatively easily obtained.

In the light of this three-dimensional analysis it has been possible to evaluate a number of the commonly used indices of ventilatory mechanics. The interrelationship between these tests has been demonstrated and an understanding of their potential variability gained. Certain areas meriting further experimental

exploration are suggested from considerations of the surface.

It is not our intent to suggest that thorough study of ventilatory mechanics requires construction of such a surface for each person. Although certain limitations of the approach are stressed, it nevertheless has proved extremely useful in visualizing these three variables simultaneously.

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Acromegaly*

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ALTHOUGH the symptom complex which constitutes the clinical entity of acromegaly was described by Marie in 1886 [1], there is a paucity of recent reports in which modern technics for the assessment of endocrine function are presented. Such methods were employed in the study of the group of patients herein described, with findings of particular importance due to the recent demonstration of the effectiveness of human growth hormone in hypopituitary dwarfs [2,3]. This review will also compare the findings before and after treatment.

METHODS

Included in this report are thirty patients who we deemed acromegalic and in whom adequate study was possible during the ten-year period from 1949 to 1958. The signs and symptoms observed in these patients are listed in Figure 1, in which the findings are compared with the data presented by Davidoff [4] in his classic study. The ages of these patients ranged from nineteen to seventy-two years, with a mean age of forty-one years. Seventeen of the thirty were women. The duration of their symptoms prior to observation on our service varied from two to forty-two years. In four of our thirty patients a family

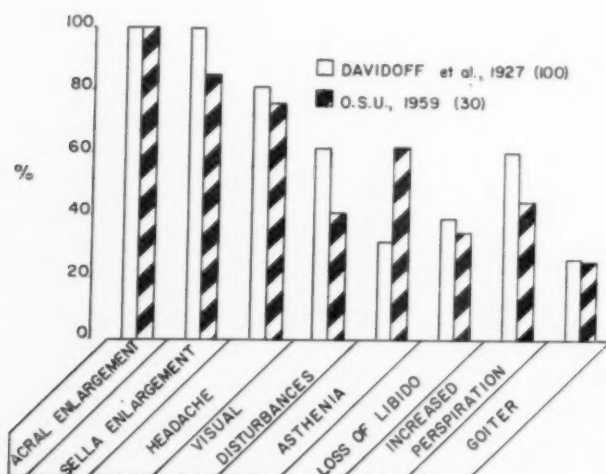


FIG. 1. Acromegaly signs and symptoms.

history of a similar disorder was obtained, although only one of a set of identical twins exhibited this disturbance.

Since the primary purpose of this study was to evaluate the alterations in endocrine function in active acromegaly, it was necessary to establish criteria of activity. The presence of one or more of the following findings was considered indicative of activity: (1) progressive acral enlargement; (2) progressive loss of visual fields; (3) persistent or progressive headaches; (4) recent onset or exacerbation of diabetes; and (5) elevation of serum phosphorus.

Using these criteria of activity, the plan of study is demonstrated in Figure 2. It will be noted that the disease was considered active in twenty-seven of the thirty patients studied and inactive in three at the time of the first admission. Of the twenty-seven patients with active acromegaly, thirteen received either x-ray or surgical treatment, two received no treatment, and twelve were considered adequately studied only for measuring the indices during activity. Eleven of the original twenty-seven patients with active acromegaly were studied again when the disease was considered inactive after periods of one to nine years. The findings in this group, with the addition of the three original inactive cases, or a total of fourteen inactive cases, were compared to the findings in the twenty-seven active cases. The methods used in these studies are those generally accepted [13-21].

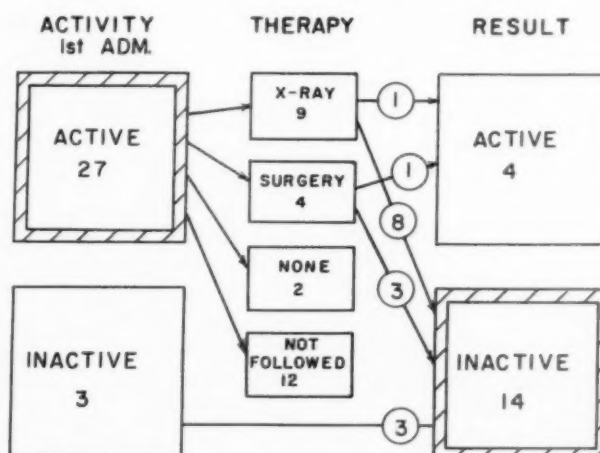


FIG. 2. Plan of study in thirty patients with acromegaly.

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RESULTS

The protean manifestations of this disorder are obvious from the presenting complaints of the patients studied. (Table 1.) Of the thirty patients only three spontaneously complained of gross changes in appearance. Although headache was the most frequent of many initial symptoms, the supposedly characteristic retrobulbar headache of pituitary tumors was present in only two patients. The specific findings related to each individual endocrine gland will be presented separately.

PITUITARY GLAND

Mechanical Effects. In spite of the fact that all patients reported were grossly acromegalic, only twenty-five of the thirty patients had definite enlargement of the sella turcica. There was no consistent correlation between the degree of enlargement of the sella and the intensity of the symptoms. A lack of correlation between the size of the sella and the incidence of visual field loss was also apparent, since two patients without gross enlargement of the sella turcica demonstrated definite visual field defects, whereas many of our patients with massive enlargement of the sella had normal visual fields.

Although only five patients presented the chief complaint of headache, on questioning 74 per cent of the patients with active acromegaly reported this symptom. Of the ten patients who had this complaint and were treated with x-ray or surgery, remission of the headache was obtained in seven. As previously mentioned, only two of the patients with active disease exhibited the so-called typical retrobulbar headache described as characteristic of pituitary tumor [5].

Visual field defects were observed in twelve of the twenty-seven active cases. In ten of these twelve patients varying degrees of bitemporal hemianopsia were found; and, as expected, the upper outer quadrants were most frequently involved. One patient had a concentric constriction of visual fields, another had a unilateral pie-shaped defect of the lower hemisphere. Another neurologic sign that was observed in one patient, who was admitted with pituitary apoplexy, was paralysis of the rectus lateralis. In a further attempt to assay neurologic function, electroencephalograms were obtained in nine patients who had received no therapy at the time of evaluation. Only three of these had abnormal electroencephalograms which showed diffuse and non-specific alterations, except in one patient who had a tracing considered char-

TABLE 1
INITIAL SYMPTOMS IN THIRTY ACROMEGALIC PATIENTS

Symptom	No. of Patients
Headache	5
Visual impairment	4
Growth of hands	3
Dyspnea	3
Diabetes	2
Knee pain	2
Malocclusion	2
Convulsion	1
Loss of consciousness	1
Acne	1
Paresthesias	1
Constipation	1
Amenorrhea	1
Abdominal pain	1
Fatigue	1
Cough	1

acteristic of grand mal. Electroencephalograms were obtained in three patients following surgery and two of these demonstrated focal abnormalities that were probably the result of the surgical intervention. Although lumbar punctures were performed in only five of our patients who were not operated upon, three of these had increased cerebral spinal fluid protein, the maximum increase being 88 mg. per cent. The chief complaint of one patient was paresthesias of the hands but it was very difficult to relate this to any specific neurologic dysfunction. Hyperostosis frontalis interna was present in every woman with acromegaly in this series but was not reported in a single man.

Pituitary Endocrine Function. Direct measurement of endocrine disturbance of the pituitary gland was limited to the determination of follicle-stimulating hormone excretion in the urine. This was performed in six patients with active acromegaly. These findings are compiled in Table II.

Gonadotropins were completely absent from the urine of three patients. One was a fifty-two year old man, another was a thirty-two year old woman, and the third was a fifty-two year old woman who had undergone bilateral oophorectomy five years prior to study. None of these individuals presented evidence of corticotropin or thyrotropin deficiency. A low titer of 6.6 mouse units was reported in a fourth patient. A year later this man had definite findings of panhypopituitarism. Titers of gona-

TABLE II
FOLLICLE-STIMULATING HORMONE TITERS IN SIX
PATIENTS WITH ACTIVE ACROMEGALY

Patient	Sex, Age (yr.)	Radio- iodine Uptake (per cent)	17-Hydroxy- corticosteroids (mg./24 hr.)	Titer (mouse units)				
				6.6	13.2	26.4	52.8	100
M. K.	F, 52	26	13.5	0	0	0	0	0
N. S.	F, 35	30	11.1	0	0	0	0	0
F. F.	M, 54	20	9.3	0	0	0	0	0
M. B.	M, 50	30	4.1	+	0	0	0	0
O. B.	M, 51	42	8.5	+	+	+	0	0
H. C.	F, 43	36	6.6	+	+	+	0	0

dotropins were within the expected normal ranges in the two other patients in whom this determination was made. These findings suggest that unitropic pituitary failure may occur in patients with acromegaly, just as in patients with non-functioning pituitary tumors such as chromophobe adenoma.

It has recently been demonstrated that, in man, injection of human growth hormone rapidly causes an elevation in serum phosphorus and a decrease in blood urea nitrogen [3]. The blood urea nitrogen averaged 12 mg. per cent in patients with active disease and 15.8 mg. per cent in patients with inactive disease. This is not statistically significant ($P > 0.05$) and proved of no value in assaying activity.

The most significant chemical alteration found was the alteration in the serum inorganic phosphorus. The average serum phosphorus in the patients with active acromegaly was 5.3 mg. per cent, with a range from 4.1 to 7.4 mg. per cent. In many patients in whom repeated serum phosphorus determinations were obtained the elevations were not persistent or constant. (Fig. 3.) In the inactive cases the range of serum phosphorus was usually within normal limits, varying from 2.8 mg. per cent to 5.2 mg. per cent and averaging 4.2 mg. per cent. Increased serum inorganic phosphorus remains the most consistent and characteristic chemical abnormality in active acromegaly [6].

In none of these patients did hypopituitarism develop spontaneously. However, of two patients who received radiation, pituitary apoplexy developed in one two weeks after completion of his therapy; this required surgical intervention and he now exhibits panhypopituitarism. The second patient was grossly and actively acromegalic until the year following the completion of radiation therapy, when he became obviously defi-

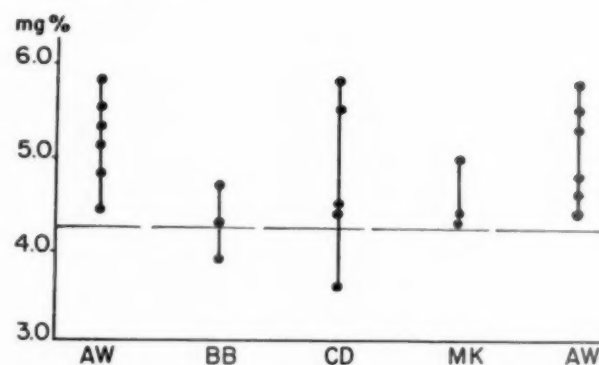


FIG. 3. Sporadic variation of serum inorganic phosphorus in patients with "active" acromegaly.

cient in all pituitary modalities. Hypopituitarism was substantiated by the development of spontaneous hypoglycemia after a fast of thirty-six hours, at which time the patient became comatose and examination revealed a blood sugar of 34 mg. per cent.

In none of the patients was lactorrhea observed on the initial admission. In one patient lactorrhea developed following radiation; this persisted for a period of three months. Although this patient had been amenorrheic prior to therapy, and amenorrhea persisted following therapy, a vaginal smear demonstrated moderate estrogenic effect.

THE POSTERIOR PITUITARY

An attempt to evaluate posterior pituitary function was made by determining the specific gravity of the urine in all the patients reported in this study. In each patient, overnight restriction of fluids resulted in a specific gravity above 1.010 (average, 1.020). The volume was not considered excessive except in one patient who had associated renal disease with uremia. In two patients the Carter-Robbins test of responsiveness to a salt load was performed and demonstrated to be within normal limits.

THYROID

Five of the twenty-seven patients with active disease had distinct non-toxic nodular goiters. An additional patient had a colloid goiter and another had a nodular toxic goiter associated with exophthalmos. This latter patient was difficult to classify since she had had a nodular goiter for many years and with the onset of her clinical manifestations of acromegaly also developed the symptomatology of thyrotoxicosis. As a consequence, the development of Graves' disease in a patient with pre-existing non-toxic nodular

goiter cannot be excluded. Unfortunately, a scintogram was not obtained. The thyrotoxicosis did not respond to adequate pituitary radiation but ultimately yielded to radioactive iodine. A history of excessive perspiration was obtained in 45 per cent of our patients but in no patient was it deemed grossly abnormal except in the patient who had associated thyrotoxicosis.

The usual laboratory indices of thyroid function proved to be of little value in assaying thyroid activity. The average basal metabolic rate in the active group was plus 6 and ranged from minus 24 to plus 41 per cent. The inactive group averaged zero per cent and ranged from minus 14 to plus 12 per cent. The serum cholesterol in our active cases averaged 195 mg. per cent (range, 110 to 285 mg. per cent) compared with an average of 217 mg. per cent in the inactive cases (range, 180 mg. to 324 mg. per cent). This variation is not statistically significant ($P < 0.1$).

The more specific indices of thyroid function were measured in practically all active and inactive cases and included the twenty-four-hour radioiodine uptake by the thyroid gland and the serum protein-bound iodine. (Fig. 4.) Repeated determinations were made in most patients but only mean values are presented. The mean radioiodine uptake for the group of patients with active acromegaly was 32 per cent, with a range from 11 to 68 per cent. There was a mean uptake of 21 per cent in the inactive group, with a range from 3 to 39 per cent. This difference is considered statistically significant, with a P value of < 0.01 . The protein-bound iodine values averaged 3.6 $\mu\text{g. per cent}$ in the active group, with a range of 0.7 to 10.5, and contrasts significantly with the mean in the inactive group of 7.1 $\mu\text{g. per cent}$, with a range of 5.2 to 10.4 ($P < 0.01$). These divergent findings apparently have not been reported previously. The conversion ratio was calculated in eight patients and averaged 16 per cent, which is within the normal range. Thus, in comparing the differences in the indices of thyroid function in patients with active and inactive acromegaly, one can conclude that in our series there is an insignificant difference in oxygen consumption, a slight but statistically insignificant decrease in serum cholesterol with activity, an increased radioiodine uptake in active compared with inactive cases, and a decrease in serum protein-bound iodine. It should be mentioned that the single clinically thyrotoxic patient was

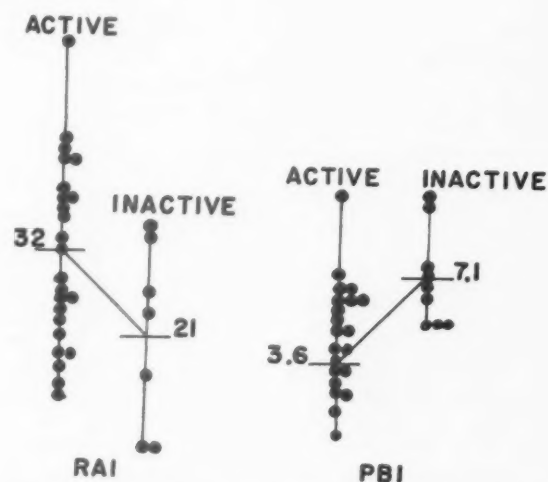


FIG. 4. Thyroid studies in acromegaly. RAI uptake expressed in per cent, PBI in $\mu\text{g. per cent}$.

found to have a protein-bound iodine of 6.1 $\mu\text{g. per cent}$, a value within the normal range and consistent with our observed depression of protein-bound iodine values in subjects with active acromegaly. These findings are different from those in a previously reported small series in which the average radioactive iodine uptake was found to be lower than normal [7].

PARATHYROID FUNCTION

In recent years there has been great interest in the association of parathyroid adenomas with pituitary tumors [8,9]. In almost all of our cases the serum calcium determinations were within normal limits. The mean value in the active cases was 10.4 mg. per cent (range 9.5 to 11.8), that of inactive cases 10.1 per cent (range 10.0 to 10.4). In two patients urinary calcium excretion studies were performed for a period of five days. The mean urinary calcium excretions averaged 90 and 92 mg. daily on a dietary intake of 150 mg. of calcium per day. These findings are within normal limits. In no patient was a history of ureteral colic or urinary calculus obtained. One patient was referred to us because of the prior diagnosis of a giant cell tumor of the mandible (epulis). The serum calcium, phosphorus, alkaline phosphatase and urinary excretion of calcium were normal, and a skeletal survey revealed no other cystic lesions.

The serum alkaline phosphatase averaged 6.1 Shinowara units in the active group (range, 3.1 to 11.3 units) and 4.9 in the inactive group (range, 3.1 to 9.3 units).

CARBOHYDRATE METABOLISM

Blood glucose studies were carried out in all patients. Poor control of diabetes was the chief

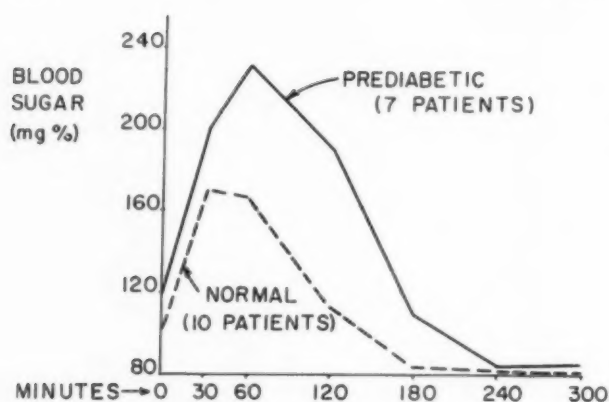


FIG. 5. Oral glucose tolerance in acromegaly.

complaint in two of the three subjects known to have symptomatic diabetes at the time of admission. In one of these patients the diagnosis of diabetes preceded that of acromegaly by five years; and at the time of initial study there was total loss of vision due to diabetic retinitis proliferans. The diagnosis of diabetes was made in a fourth patient as a result of an oral glucose tolerance test. Each of these individuals was treated with insulin at the time of discharge. The daily doses were 65, 45, 40, and 15 U. of isophane insulin and no difficulty was experienced in managing the diabetes. In no patient did a remission of the diabetes occur following treatment of the acromegaly.

In seven other patients the oral glucose tolerance curves were of the configuration best categorized as "prediabetic." (Fig. 5.) Four of these patients were restudied when the acromegaly was considered inactive and no improvement of glucose tolerance was observed. When the mean values of six glucose tolerance tests made in patients when the disease was active were compared with the findings in the same

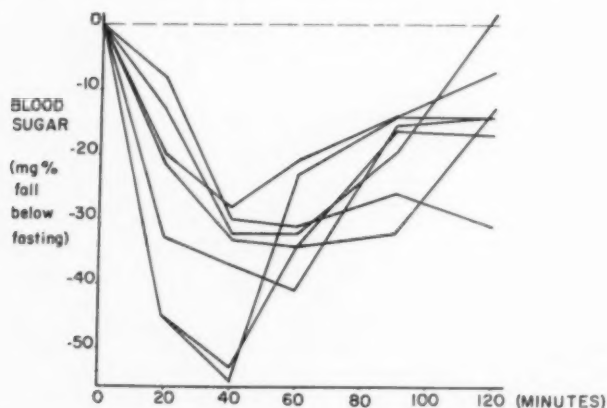


FIG. 7. Standard insulin tolerance tests in seven non-diabetic patients with acromegaly.

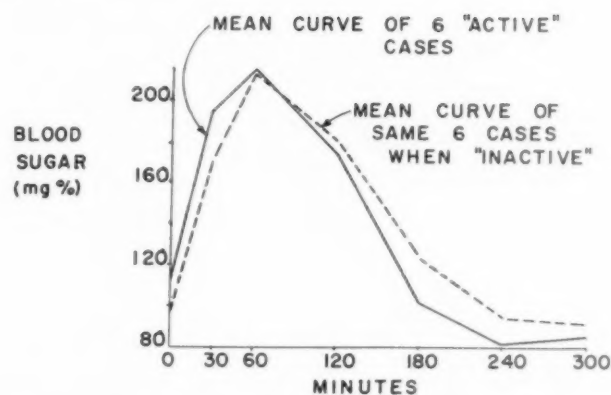


FIG. 6. Effect of control of acromegaly on oral glucose tolerance.

patients when the disease was inactive no essential changes were noted. (Fig. 6.)

The remaining sixteen patients with active disease proved to be non-diabetic. Oral glucose tolerance tests in ten of these patients were entirely within normal limits. Fasting and postprandial blood sugar values in the other six patients also were normal. The mean values of the oral glucose tolerance tests found in the seven prediabetic patients and in ten of the sixteen non-diabetic patients are depicted in Figure 5.

Intravenous insulin tolerance tests were obtained in seven of the non-diabetic patients with active acromegaly. In each instance a rather prompt and significant fall in blood sugar occurred. Forty minutes after the injection of 0.1 U./kg. of body weight of crystalline insulin a mean fall of 38 mg. per cent was observed. (Fig. 7.) The configurations of these insulin tolerance tests and the degree of fall in blood sugar observed were similar to values observed in normal non-diabetic persons. In general, the severity of the diabetic symptoms correlated fairly well with the severity of the acromegalic symptoms. Our experience suggests that once diabetes is clearly established, it persists, and control of acromegalic activity does little to alleviate intolerance to ingested glucose. It is perhaps pertinent that sensitivity to small doses of intravenously administered crystalline insulin is maintained in non-diabetic patients with active acromegaly.

THE ADRENAL GLANDS

Enlargement of the adrenal glands has been reported as a postmortem finding in acromegaly [10]. In our series, none of the twenty-seven patients with active disease presented evidence for either hypersecretion or hyposecretion of

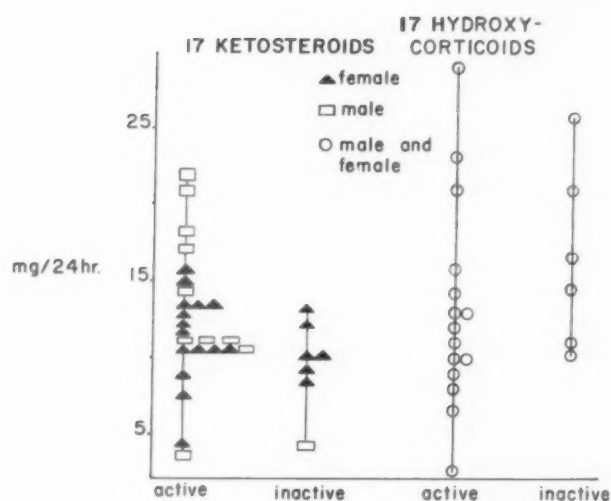


FIG. 8. Adrenal cortical function in acromegaly.

adrenal cortical hormones. As noted, subsequent panhypopituitarism developed in two male patients. In one instance this was secondary to surgical intervention and the other occurred following radiation.

A total of 167 determinations of the twenty-four hour urinary excretion of neutral 17-ketosteroids and 140 determinations of urinary 17-hydroxycorticosteroids were performed. In Figure 8 the average values in patients with active disease are compared with the average values in patients with inactive disease. In addition, tests utilizing ACTH for the determination of adrenal responsiveness, as measured by the excretion of these moieties, were performed. The values for 17-ketosteroids in the fifteen female patients believed to have active acromegaly averaged 11.5 mg. per day, with a range within the normal limits of 5 to 15 mg. per day. Studies made on seven female patients with inactive disease yielded similar results (average, 10.6 mg.; range, 8.7 to 12.3 mg./day), as did those on male patients with inactive disease (average, 15.2 mg. per day; range, 8 to 22).

The mean daily urinary excretion of hydroxycorticosteroids in fifteen patients of both sexes with active disease was 13.3 mg., with a range from 6.6 to 23.6 mg./day, except in one patient in whom the excretion averaged only 2.5 mg./day. Stimulation of the adrenal cortex by means of a six-hour intravenous corticotropin drip was carried out in five patients. (Fig. 9.) Four responded in a fashion characteristic of the normal, with a two- to fourfold increase in total corticoid output. In one patient the twenty-four-hour excretion increased from 16 to 79 mg., which

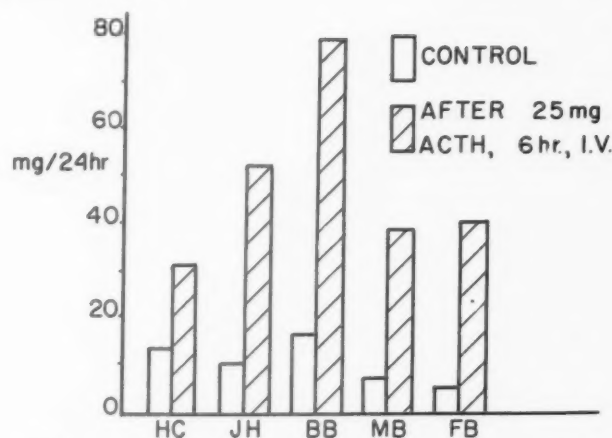


FIG. 9. Response of urinary 17-hydroxycorticosteroids to ACTH in acromegaly.

might be considered an exaggerated response to this stimulus. The single patient with abnormally low corticoid excretion responded normally to ACTH, increasing from 2.5 to 40 mg. per day. Studies in these patients during the inactive phase of their acromegaly showed no statistically significant differences from those made during the active phase (values for the two patients in whom hypopituitarism developed were not included in these calculations). In addition to these direct laboratory indices of adrenal function, repeated determinations of serum sodium, potassium, chloride and carbon dioxide combining power were entirely within normal limits.

In summary, no significant deviations of adrenal function were encountered.

THE ADRENAL MEDULLA

No findings suggestive of increased activity of the adrenal medulla were obtained. When histamine stimulation, benzodioxane or phenolamine testing was performed, normal responses consistently occurred. Unfortunately, urinary catecholamines were not measured.

GONADS

A history of impotence was obtained from three of the thirteen men with acromegaly. Decreased libido was present in eleven of the thirty patients studied. These subjective data are, of course, of uncertain significance.

With regard to objective indices of gonadal function in the men, no patient demonstrated atrophic changes of the prostate, penis or testes. Semen analyses were not performed. The excretion of 17-ketosteroids, already summarized, averaged the expected 30 per cent higher in men than in women.

TABLE III
ASSOCIATED DISEASES

Disease	No. of Patients
Hypertensive heart disease	10
Pre-diabetes	7
Non-toxic nodular goiter	5
Diabetes	4
Myocardial infarction	4
Symptomatic osteoarthritis	4
Osteoporosis	3
Megacolon	3
Benign prostatic hypertrophy	2
Active duodenal ulcer	2
Cholelithiasis	2
Chronic pyelonephritis	2
Colloid goiter	1
Toxic nodular goiter	1
Epulis	1
Fibromyoma uterus	1
Carcinoma of cervix	1
Endometrial polyps	1
Adenocarcinoma of kidney	1
Obstructive emphysema	1
Bronchial asthma	1
Congenital absence of kidney	1

In the seventeen women there was a multiplicity of complaints relating to the genital tract. Three patients complained of amenorrhea, four of menorrhagia, one of oligomenorrhea, and one of irregular menses. A large proportion of our female patients had been subjected to hysterectomy (seven of seventeen, or 41 per cent). In three instances hysterectomy had been performed for neoplasms (fibromyoma, carcinoma of the cervix and endometrial polyps). Three of the remaining four patients were subjected to hysterectomy to correct excessive uterine bleeding. Physical examination on admission revealed the presence of an enlarged clitoris in two patients.

No impairment of fertility was manifested as only two of the sixteen married acromegalic patients were barren.

ASSOCIATED DISEASES

Associated diseases observed in our series are tabulated in Table III.

Hypertension and Cardiomegaly. Ten (37 per cent) of the twenty-seven patients with active acromegaly were found to have sustained diastolic hypertension (>100 mm. Hg). Eight of these individuals demonstrated enlargement of the cardiac silhouette when studied by teleroentgenography of the chest. Four of the

eight patients showed enlargement of the left ventricle by electrocardiography and fluoroscopy, while the other four were found to have generalized cardiomegaly associated with congestive heart failure. In four instances the pattern of myocardial infarction was found by electrocardiography. Two patients with hypertension had a normal heart size: one was a twenty-six year old man who had had acromegaly for five years and the other was a fifty-seven year old woman with associated diabetes. Of the ten patients demonstrating cardiomegaly, only two were normotensive. One of these had congestive heart failure secondary to a large myocardial infarction, the other had minimal cardiomegaly.

Since congestive heart failure is listed as a frequent cause of death in acromegaly [11,12], enlargement of the heart may not be merely a reflection of the visceromegaly common to this syndrome. Our data strongly suggest that cardiomegaly in the patient without congestive failure is secondary to hypertension and/or myocardial infarction, and is characterized by left ventricular enlargement.

The etiology of hypertension in acromegaly is obscure. In two of our patients it was clearly of renal origin: both suffered from chronic pyelonephritis and one of them had previously undergone nephrectomy for removal of a hypernephroma. In other patients no specific endocrine basis for hypertension was suggested in spite of repeated phentolamine or histamine tests, excretory urography and careful study of adrenal and thyroid function.

All three of the patients considered to have inactive acromegaly at the first visit showed congestive heart failure. Two of these were hypertensive, and the third had electrocardiographic evidence of an old myocardial infarction. These three patients were all in the older age group, the youngest being fifty-eight years of age.

Osteoarthritis. Manifestations of degenerative joint disease were found in 74 per cent of the patients. In four patients these symptoms were of sufficient severity to be disabling and in two patients warranted surgical intervention. The disabling symptoms were encountered in weight bearing joints.

Neoplasms. Six of the thirty patients had new growths. In two patients they were malignant: one had a carcinoma of the cervix at age thirty-six, and one an adenocarcinoma of the kidney at

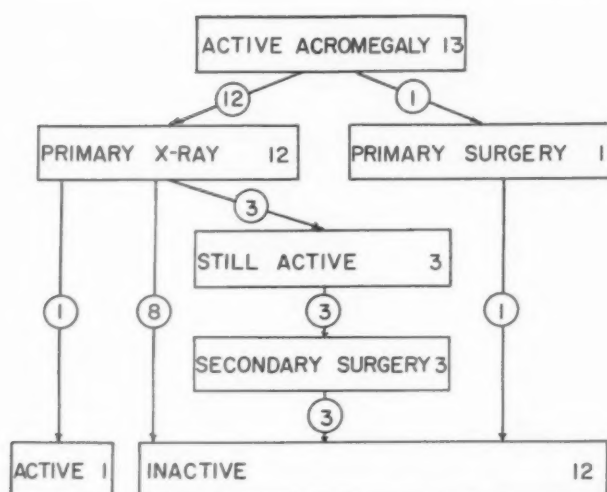


FIG. 10. Results of therapy on the activity of thirteen patients with acromegaly.

age thirty-nine. There were two patients with benign prostatic hypertrophy, and one each with epulis, papilloma of the larynx, and mediastinal cyst. These are in addition to the fibromyoma and uterine polyps already mentioned.

Osteoporosis. Demineralization of the vertebrae was diagnosed by roentgenographic examination in three patients. In only one patient was this finding symptomatic, and this individual was a sixty-nine year old man whose height had decreased 6 inches due to multiple vertebral compression fractures. The other two patients were women, aged forty-two and sixty-two.

Gastrointestinal System. Seven patients had abnormalities in the gastrointestinal system. In two patients active duodenal ulcers were demonstrated by roentgenograms. One of these had gastrointestinal bleeding and the other was unusual in that the ulcer was diagnosed when the patient was sixty-nine years of age. In the latter patient gastric analysis demonstrated 64° of free acid. Two patients had cholelithiasis.

Three patients demonstrated varying degrees of abnormal enlargement of the colon. In one patient the enlargement was primarily limited to the cecum, whereas the other two had generalized enlargement of the colon. One of these patients required 8 L. of barium to visualize the colon adequately.

Respiratory System. Eighteen of the thirty patients studied were considered to have a barrel chest but only one had obstructive pulmonary emphysema, and another had bronchial asthma.

Genitourinary System. There were two patients with severe chronic pyelonephritis, and one ultimately died of uremia (the only known death

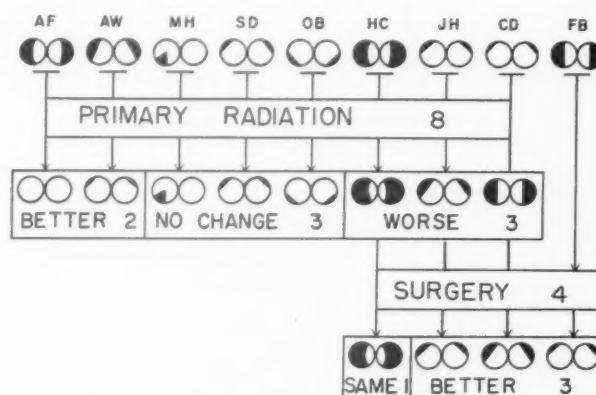


FIG. 11. Effect of therapy on visual fields.

in this series). One patient was found to have congenital absence of one kidney. The two cases of benign prostatic hypertrophy, and one of adenocarcinoma of the kidney have already been mentioned.

Evaluation of Therapy. Of the twenty-seven patients with active disease thirteen received either x-ray or surgical treatment, the results of which could be adequately assessed. Patients were not treated, even if the disease was considered active, unless they complained of associated disabling symptomatology which usually consisted of a progressive disturbance in vision or persistent or progressive headaches. In one patient marked exacerbation of a pre-existing mild diabetes following surgery to the pituitary, was considered justification for radiation therapy. (Fig. 10.)

The initial therapy utilized was x-ray except in one patient who was considered a neurosurgical emergency. Varying roentgenographic techniques were used during the period of this study, but in general a tumor dose of at least 3,500 r was attempted in each patient treated. Twelve patients with active disease received x-ray treatment initially. Eight of these patients, re-evaluated within periods of one to nine years, were considered inactive. Of these, five had originally demonstrated visual field defects. In two of the five patients with visual field defects marked improvement occurred, while in the remaining three patients no change was demonstrated. Three of the twelve patients with active disease treated with x-ray required surgical intervention. In two, this was deemed advisable due to progressive loss of vision, in the other because of pituitary apoplexy. One patient treated with x-ray in 1952 and re-evaluated in 1959 still is considered to have active acromegaly. (Fig. 11.)

TABLE IV
A SUMMARY OF VARIOUS LABORATORY FINDINGS IN ACTIVE AND INACTIVE ACROMEGALY*

Laboratory Test	Active (27 patients)	Inactive (14 patients)	P
Serum inorganic phosphorus (mg. per cent)	5.3 (4.1-7.4)	4.2 (2.8-5.2)	<0.01
Serum calcium (mg. per cent)	10.4 (9.5-11.8)	10.1 (10.0-10.4)	>0.10
Serum alkaline phosphatase (Shinowara units)	6.1 (2.3-11.3)	4.9 (3.1-9.3)	>0.10
Blood urea nitrogen (mg. per cent)	12.0 (8-20)	15.8 (8-28)	>0.05
17-Ketosteroid excretion (mg./24 hr.)	12.2 (3.1-22.0)	9.3 (3.5-13.3)	>0.10
17-Hydroxycorticoid excretion (mg./24 hr.)	13.3 (2.5-29.0)	16.6 (11.1-25.8)	>0.10
Protein-bound iodine (μ g. per cent)	3.6 (0.7-10.5)	7.1 (5.2-10.4)	<0.01
24-hour radioiodine uptake (per cent)	32 (11-68)	21 (3-39)	<0.01
Basal metabolic rate (per cent)	+6 (-26 to +41)	0 (-14 to +12)	>0.10
Serum cholesterol (mg. per cent)	195 (110-285)	217 (217-324)	>0.10

* Numbers in parentheses indicate ranges.

In the single instance in which surgery was used as the initial mode of treatment the indication was marked loss of the visual fields. This was dramatically improved by the surgical intervention.

All of the four patients treated by surgery exhibited visual field defects, and three improved. The vision of the fourth patient was unchanged by surgery. In one patient in each therapeutic group hypopituitarism developed.

It should be emphasized that in no instance did control of activity by therapy significantly alter the severity of the diabetes or hypertension once these complications became firmly established.

SUMMARY

Twenty-seven of thirty patients with acromegaly were considered to be actively secreting excessive growth hormone according to the following criteria: (1) progressive acral enlargement; (2) progressive loss of visual fields; (3) persistent headaches; (4) recent onset or exacerbation of diabetes mellitus; (5) elevation of serum inorganic phosphorus. The clinical and laboratory findings of the twenty-seven patients with active disease were compared with the findings of these patients after treatment, and with those in other (untreated) patients in whom the disease was considered inactive. Fourteen cases comprised the inactive group.

Clinically, the patients presented a wide variety of complaints, with a non-characteristic headache as the most frequent symptom. There was no relation between the size of the sella and intensity of symptoms or frequency of visual

field loss. Five of thirty patients did not have a grossly enlarged sella turcica by roentgenographic examination. Visual field defects were found in twelve of twenty-seven active cases.

Table IV summarizes laboratory data. Follicle-stimulating hormone was absent from the urine or present in diminished quantity in four of the six patients tested. No significant difference was found in the blood urea nitrogen levels of the patients with active and inactive disease. The serum inorganic phosphorus, however, was higher in the former group.

Seven of twenty-seven patients had thyroid enlargement and one of the seven had the classic manifestations of thyrotoxicosis and exophthalmos with a nodular goiter. The twenty-four-hour radioactive iodine uptake was higher and the serum protein-bound iodine was lower than in the inactive group.

Four patients were overtly diabetic and seven patients had prediabetic glucose tolerance tests; thus eleven of twenty-seven patients with active disease had some impairment of carbohydrate metabolism. In six patients with abnormal glucose tolerance tests prior to therapy, re-evaluation of carbohydrate metabolism revealed no improvement after the patients were treated and acromegaly considered inactive.

No gross differences between the patients with active and inactive disease could be found in the urinary excretion of 17-ketosteroids and 17-hydroxycorticoids.

No gross objective abnormalities were found in the gonadal function of thirteen men with acromegaly; however, nine of seventeen women had menstrual disturbances. Studies of the posterior

pituitary, parathyroids and adrenal medulla yielded no evidence of altered function.

Ten of twenty-seven patients with active acromegaly had sustained diastolic hypertension. Of these, eight had cardiomegaly. Two patients had cardiomegaly in the absence of hypertension, one due to myocardial infarction.

Of thirteen patients with active acromegaly, twelve were subjected to x-ray therapy. In eight of these the disease became inactive. Three of the four remaining patients were subjected to surgery due to progressive deterioration in vision and, in a single instance, to pituitary apoplexy. In one patient in each of the two treatment groups panhypopituitarism ultimately developed.

Eight of the nine patients with active disease and visual field defects were treated by radiation. Two had definite improvement in their visual fields, three remained unchanged, and definite deterioration in vision occurred in three. The latter three patients and one patient who had marked impairment of vision when first seen were treated surgically. The visual field improved in the first three and remained unchanged in the latter.

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Clinicopathologic Conference

Friedländer Pneumonia, Hypocalcemia and Renal Failure

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was an eighty-two year old white housewife, who was admitted to Barnes Hospital for the fifth time on December 7, 1956 and died on January 13, 1957. Her first hospital admission was on January 1, 1941 to February 19, 1941. The diagnosis was acute cholecystitis, cholelithiasis and generalized arteriosclerosis. A cholecystectomy was performed. Her second hospital admission was on February 9, 1942 to March 7, 1942. The diagnosis was chronic neuritis of sciatic nerve and hypertrophic osteoarthritis. Her third hospital admission was on October 9, 1945 to October 24, 1945. Diagnosis was carcinoma of the breast and a simple excision of mammary gland was performed. Her fourth hospital admission was on March 9, 1954 to April 19, 1954 for "bruises" of three days' duration.

Except for the intermittent presence of diarrhea for many years, which had been adequately controlled with diet and the administration of bismuth, and a minimal, constant aching in her ankles for the past few months, the patient was apparently well until three days prior to admission. At this time she noted large ecchymotic areas periorbitally, on the left elbow and the right forehead. One day prior to admission, she noted the eruption of a large ecchymosis on the medial aspect of the right knee, and the development of numerous small ecchymoses over the extremities rapidly followed. She complained only of a slight cold and sore throat, but denied any history of fever, chills, or bleeding. Except for the use of salicylates during the last few months for an ache in her ankle, she denied any intake of drugs.

The patient had intermittent episodes of diarrhea for many years. There was no history of abdominal pain, nausea, vomiting, hematemesis,

or melena associated with these episodes, though blood was occasionally present at the end of a bowel movement. Her physician believed that the diarrhea was indicative of an idiosyncrasy to some foods and had maintained her on dietary and bismuth therapy. The records of her first three hospitalizations were not available. The patient admitted to the intake of alcohol, but denied any history of smoking. The patient's mother died at the age of sixty-two years with diabetes mellitus.

Physical examination revealed a blood pressure of 180/90 mm. Hg, a pulse of 90, respirations of 20, and a temperature of 36.7°C. The patient was a well developed, elderly white woman in no acute distress with large ecchymoses around the right eye, left forearm, flexor surface of right forearm, right thigh and knee. There were no petechiae. Her pharynx was injected and she had lenticular opacities bilaterally. There was dorsal kyphoscoliosis with an increase in the posteroanterior diameter of the thorax. The point of maximal impulse of the heart was in the sixth intercostal space at the anterior axillary line and there was a grade 3/6 blowing apical systolic murmur. Except for puffiness and tenderness of the right ankle the remainder of the examination revealed no abnormalities.

Laboratory data were as follows: the hemoglobin was 12.6 gm. per cent, the packed cell volume 42 per cent, white blood cell count 9,250 per cu. mm. with 43 per cent segmented forms, 1 per cent stabs, and 56 per cent lymphocytes. The urine had a specific gravity of 1.021, pH 5.0, trace protein and negative sugar reaction; examination of the centrifuged urinary sediment revealed two to four white blood cells per high power field. The blood cardioli-

reaction was negative. Stool examination on admission had negative results for occult blood and neutral fat. Normal values were reported for the serum proteins, non-protein nitrogen, fasting blood sugar, prothrombin time, cephalin-cholesterol flocculation, thymol turbidity, alkaline phosphatase and reticulocyte and platelet counts. Clot retraction was normal as was the bleeding time, the silicone clotting time, and the tourniquet test. Roentgenograms of the chest were interpreted as showing moderate cardiac enlargement, left ventricular enlargement, pulmonary emphysema and old fracture deformities of the right rib cage and clavicle. The electrocardiogram was interpreted as normal with auricular and ventricular premature contractions.

The patient was subjected to skin scratch and patch tests for numerous drugs and chemicals with which she had contact; all gave negative results except for chloral hydrate which had positive results; this occurred in the control subject as well. After the first six days of hospitalization, no new areas of purpura appeared and, except for the appearance of pain in her left shoulder area the patient improved and was discharged.

Her fifth hospital admission was on December 7, 1956 to January 13, 1957 for fever of two days' duration. The patient was unable to give any history, but apparently had done well except for the presence of a chronic mild, non-productive cough which had become worse during the two days immediately prior to her admission. During this latter period, she noted bloody sputum and complained of a sore throat, upper chest pain, and fever. There was no history of chills, night sweats, abdominal pain, nausea, vomiting, back pain, or dysuria.

Physical examination revealed the following: blood pressure 160/80 mm. Hg, pulse 86, respirations 26, temperature 38.4°C. The patient was an elderly, dehydrated white woman, who was poorly responsive, confused, and at times, antagonistic. Her skin was warm and dry with poor turgor. Her tongue was beefy-red and dry. She had lenticular opacities bilaterally. There was dorsal kyphoscoliosis with an increase in the posteroanterior diameter of the thorax. There were scattered rales and rhonchi in both lung fields posteriorly. The heart could not be examined adequately. The remainder of the examination revealed no abnormalities.

Laboratory data were as follows: the hemo-

globin was 11.4 gm. per cent, white blood cell count 9,950 per cu. mm. with 72 per cent segmented forms, 26 per cent lymphocytes, and 2 per cent monocytes. The urine had a specific gravity of 1.021, pH 4.5, trace protein and negative sugar reaction; examination of the centrifuged urinary sediment showed an occasional white blood cell per high power field. The admission and subsequent stool examinations had negative results for occult blood and neutral fat. Non-standard roentgenograms of the chest were interpreted as showing no gross abnormalities of the heart and lungs, but both examinations were taken in expiration. The electrocardiogram was said to show an abnormal form of ventricular complex and first degree auriculo-ventricular heart block. Sputum culture demonstrated gram-negative, lactose fermenting rods which were mucoid in appearance; its administration killed a mouse in thirty-six hours. It was believed to be compatible with *klebsiella*. The report of antibiotic sensitivity tests showed that there was no growth of the organism in 1.5 µg. per cc. of Aureomycin® and Terramycin®, 0.025 units per cc. of penicillin, 0.025 µg. per cc. of Achromycin® and streptomycin, and 20 µg. per cc. of Chloromycetin®. There was a heavy growth of *pyocyaneus* on culture of the urine and no growth on culture of the blood. The fasting blood sugar was 116 mg. per cent, serum non-protein nitrogen 29 mg. per cent, sodium 153 mEq. per L., potassium 3.4 mEq. per L., carbon dioxide 25.2 mEq./L., chloride 116 mEq. per L., calcium 6.2 mg. per cent, phosphorus 4.3 mg. per cent, alkaline phosphatase 5.6 Bodansky units, albumin 3.7 gm. per cent and globulin 2.1 gm. per cent (repeat value was 2.5 gm. per cent). (Fig. 1.)

The administration of aqueous penicillin was begun but the patient continued to have nightly temperature elevations up to 39.8°C. during the first six days of hospitalization. On the fifth day, a seven-day course of Achromycin and a twenty-seven-day course of Dicrysticin® was initiated. During this period the patient remained seriously ill and demonstrated a decreased output of urine, although incontinence prevented its quantitation. During the fifth day the patient had a grand mal convulsion, which was followed by the appearance of cyanosis, stupor, generalized muscle rigidity and resistance to passive motion. Therapy with intravenously administered fluids, calcium gluconate, potassium chloride, and vitamins was instituted. On the next day the

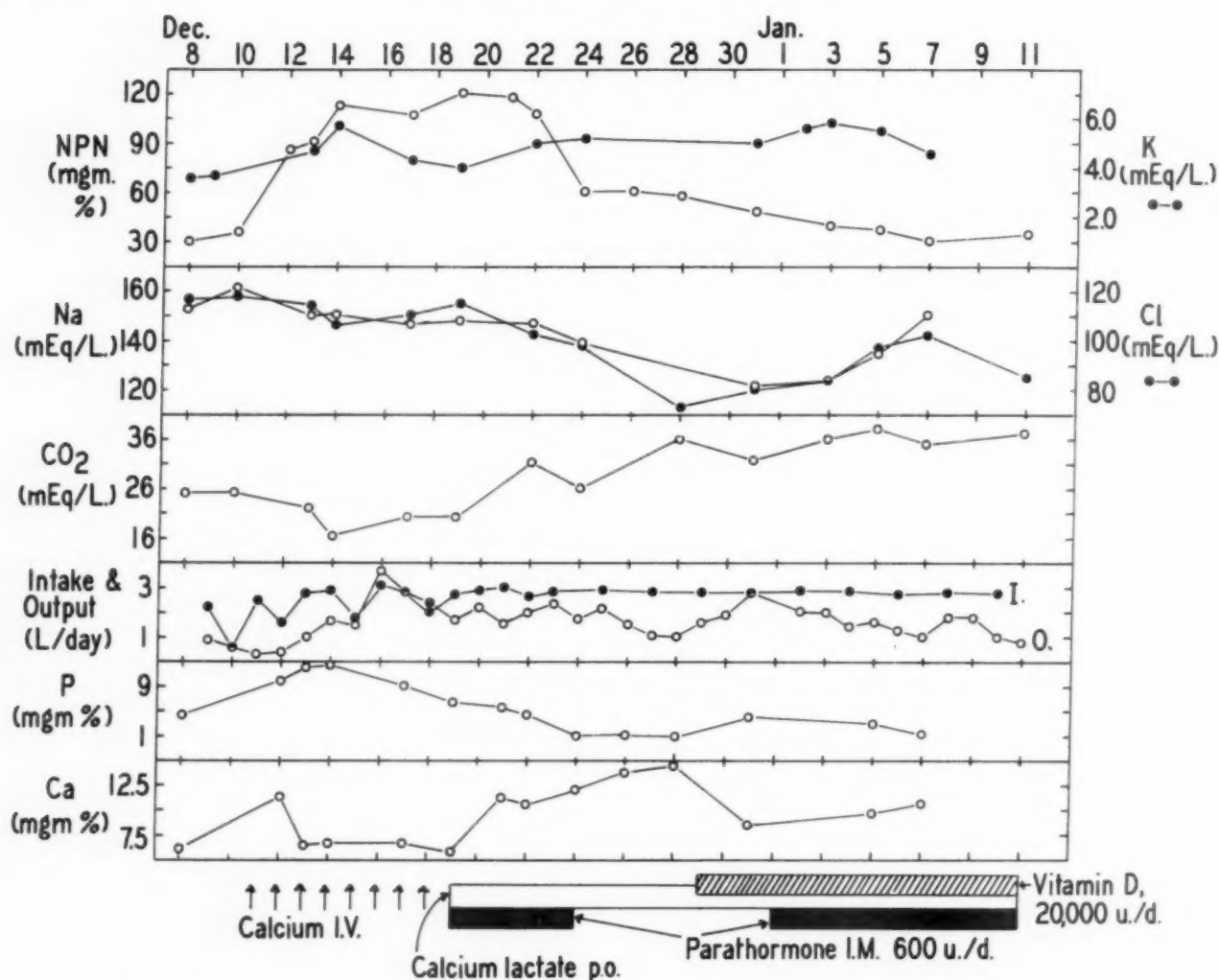


FIG. 1. Graphic representation of the laboratory observations during the last hospital admission.

serum non-protein nitrogen was 86 mg. per cent, calcium 11.4 mg. per cent, phosphorus 10.5 mg. per cent, and the white blood cell count was 14,650 per cu. mm. Repeat blood culture revealed no growth and urine culture demonstrated only one colony of pyocyaneus. Examination of the urine was unchanged except for the presence of five to ten white blood cells per high power field in the centrifuged urinary sediment. There were signs of pneumonia of the left lower lobe of the lung on physical examination at this time. Fluids were intravenously administered throughout the second week. Concomitant with a daily output of urine ranging from 975 cc. to 3,575 cc. there was a progressive rise in the non-protein nitrogen during the next six days to a maximum of 121 mg. per cent December 19. The remainder of the chemistry values, except for a falling of CO₂ capacity (20.2 mEq. per L.), approximated the values noted on admis-

sion. The prothrombin time was 48 per cent of normal and the cephalin-cholesterol flocculation was 3 plus. The temperature ranged between 38° and 37°C. during the second week (it remained normal throughout the rest of her hospitalization). The patient became less stuporous, although some confusion remained. Lumbar puncture and examination of the spinal fluid demonstrated no abnormalities. Muscle rigidity was less marked.

On the thirteenth hospital day the patient was begun on tube feedings which, in addition to dietary constituents, contained calcium lactate, Parentesol,[®] paregoric, and Sulfasuxidine.[®] Parathyroid extract was given intramuscularly. During the next week the pneumonic process was believed to have cleared and the white blood cell count fell to 10,000 per cu. mm. Tetany, which had not been controlled by calcium gluconate, was somewhat relieved by para-

thyroid extract. The patient now appeared semicomatose; she was restless but unresponsive. A progressive decrease in the non-protein nitrogen (65 mg. per cent) and phosphorus (1.3 mg. per cent) had occurred by the nineteenth day. During this period, the blood calcium ranged from 10.6 mg. per cent to 13.8 mg. per cent and the blood sugars from 164 mg. per cent to 435 mg. per cent. No evidence of glycosuria was obtained on the daily Clinitest® examinations.

During the fourth and fifth weeks of hospitalization (December 28 to January 10) there was no change in the physical status of the patient except for the transient appearance of a generalized skin rash. The blood non-protein nitrogen had fallen to 26 mg. per cent, the fasting blood sugar to 80 mg. per cent and the remaining blood chemistry values showed only minor alterations. The white blood cell count and urinalysis were within normal limits.

On January 11 (the beginning of the sixth week) the blood pressure was noted to have fallen from the usual 175/60 to 130/50 mm. Hg and was accompanied by a marked increase in stupor. Neurological examination revealed absent knee and ankle jerks bilaterally, generalized rigidity of the extremities, greater in the arms, anesthesia of the right hand, and a general withdrawal of both legs and the left hand in response to a non-specific painful stimulus. On January 12 the urine output fell to 650 cc., the systolic blood pressure ranged from 70 to 100 mm. Hg, respirations became irregular and there was a rapid increase in the depth of her coma. She died quietly on January 13.

CLINICAL DISCUSSION

DR. SOL SHERRY: The patient discussed today presented us with a diagnostic problem. She had had five admissions to Barnes Hospital. The first three were in the early 1940's and the records were unavailable. In 1954 at seventy-nine years of age she entered the hospital with a purpuric eruption, of unknown etiology, which spontaneously subsided. Upon discharge it was believed that the illness represented a drug purpura. In December 1956 at the age of eighty-two, she was admitted to the hospital critically ill with a febrile disease believed to be Friedländer pneumonia. Her course was complicated by severe hypocalcemia, neurological difficulties, transient renal failure, and all types of electrolyte abnormalities and fluctuating hyperglycemia.

Although her fever subsided, she always remained seriously ill. She died during the sixth week of hospitalization after a fall in blood pressure and an aggravation of her neurological abnormalities. Dr. Walsh has been kind enough to summarize her electrolyte findings in chart form. (Fig. 1.) Dr. Brown will present the roentgenographic findings.

DR. MARK BROWN: Two roentgenographic examinations of the chest were performed on this patient. The first one was taken shortly after the next to last admission. This shows cardiac enlargement that is primarily left ventricular. The lung fields are somewhat emphysematous. There is an abnormality of the distal right clavicle which is consistent with an old fracture. There is also a deformity along the right rib cage, again thought to be due to old fractures. The second set of films were taken on the last admission and were supine because of the patient's poor condition. Again the changes in the distal right clavicle and the right rib cage are noted. No change occurred in the two-year interval. The cardiac enlargement is as before. In spite of the clumping of the vessels due to expiration there is superimposed upon this some infiltration in both lower lobes, particularly in the left, consistent with pneumonia.

DR. SHERRY: What about the state of the bones, other than the old fractures?

DR. BROWN: On the lateral film of the initial examination, osteoporosis with generalized demineralization and hypertrophic changes in the dorsal spine are seen. I do not believe we can go any further than that on these examinations. She was eighty-two years old and the demineralization is consistent with her age.

DR. SHERRY: Do you believe the fractures were on a traumatic basis?

DR. BROWN: I think so. This would be a very unusual place for a pseudofracture. If this were metastatic, it should have changed over a two-year period.

DR. SHERRY: Dr. Noah, during the patient's admission in 1954, a diagnosis of drug purpura was made. In retrospect, are you satisfied that this patient had a drug purpura?

DR. JOSEPH NOAH: I think that it is likely.

DR. SHERRY: In patients with gastrointestinal disorders, as a consequence of possible peculiarities in absorption, are drug purpuras more likely to develop. I raise this point since our patient may have had an underlying gastro-

intestinal disorder as suggested by her history of chronic intermittent diarrhea.

DR. NOAH: In persons who have a familial and personal tendency to allergic reactions, drug reactions are likely to develop. If we accept this patient's intermittent diarrhea as an instance of allergy to certain foods, then this would be one point in favor of the allergic origin of the purpura.

DR. SHERRY: Has the mechanism of allergic purpuras been established?

DR. NOAH: It is thought that in patients in whom the platelet count is within normal limits, the defect occurs in the capillaries. However, as far as I am aware this has not been established on an anatomical or histologic basis.

DR. SHERRY: When our patient was admitted to the hospital on her final admission, it was believed that she had a Friedländer's pneumonia. Dr. Harford, are you satisfied with this diagnosis?

DR. CARL G. HARFORD: I think that the reason for suspecting this diagnosis was that cultures of sputum contained mucoid colonies of bacteria that fermented lactose, and were pathogenic for mice. However, there are two major difficulties. In the first place, it was apparently not determined whether the organism had a capsule nor was a Quellung reaction carried out with capsular antiserums, although some of such antiserums are available. The information is, therefore, not complete enough for us to know whether or not this organism was a Friedländer's bacillus. Coliform bacteria with mucoid colonies are often cultivated from sputum of patients with pulmonary infection; it is not at all certain that these organisms are causing pulmonary infection. In fact, similar bacteria are frequently obtained from sputa of patients who do not have any evidence of pulmonary infection. Therefore, I do not think that the present bacteriological evidence is sufficient for us to make a diagnosis of Friedländer's pneumonia or to know whether or not the patient had bacterial infection of the lungs.

DR. SHERRY: Are we seeing a different type of Friedländer's pneumonia in hospitals today as contrasted with the classic description of a patient who is desperately ill, with very thick "currant jelly," or mucoid sputum, and extensive boggy infiltrates in the lung?

DR. HARFORD: I cannot say whether or not the patterns are changing. I do know that encapsulated coliform bacilli that produce mucoid

colonies and are pathogenic for mice are isolated from sputum quite frequently. Sometimes the patients have pneumonia and sometimes they do not. The clinical picture associated with these organisms is usually not what you have just mentioned.

DR. SHERRY: Some physicians differentiate between acute and chronic Friedländer pneumonias; it is said that chronic Friedländer pneumonias may give a picture resembling bronchiectasis or pulmonary tuberculosis. Do you make that differentiation?

DR. HARFORD: I have read papers concerning chronic pulmonary infections with this type of organism. However, I think that simply cultivating such bacteria from the sputum is not adequate evidence to indicate that these organisms are actually causing pulmonary infection.

DR. SHERRY: Dr. Kipnis, some reports state that diabetes is associated with Friedländer's pneumonia with an incidence as high as 20 per cent. On the basis of the data available do you believe our patient was a diabetic and how well documented is this association?

DR. DAVID KIPNIS: I believe the patient did have mild diabetes and that the degree of hyperglycemia and hence the consequent glycosuria paralleled the severity of her illness. When the fever abated and the pulmonary infection apparently cleared, the blood sugars returned toward normal levels. The accentuation of intolerance to carbohydrates associated with infections is well documented and I think that we have a case in point. It is still not clearly established whether patients with diabetes are predisposed to Friedländer bacillus infections or whether series of patients with Friedländer infections have a high incidence of diabetes. For example, reports can be found reviewing 20,000 consecutive diabetic patients at the Baker clinic where only two patients with Friedländer infection were observed. This is well within the expected incidence in a general hospital population.

DR. SHERRY: Dr. Harford, our patient had a high fever, and when she was treated with antibiotics her fever subsided and she remained fairly normal for the last few weeks of her illness. Under such circumstances, is it still possible that she could have had an initial infection, for example in her lungs, which disseminated to her brain or elsewhere and caused her death?

DR. HARFORD: I think she could have had metastatic infectious foci, or the presence and

persistence of a pulmonary infection may have been a factor which contributed to her death.

DR. SHERRY: Would the fact that the patient became afebrile with a disappearance of leukocytosis rule out such a complication?

DR. HARFORD: No. This happens frequently, especially in older people and in people who are extremely debilitated.

DR. SHERRY: Dr. Levy, what do you think of the possibility that a brain abscess developed in this patient which smouldered along and finally caused her death?

DR. IRWIN LEVY: I suppose it is possible, but there is no evidence to support such a supposition.

DR. SHERRY: Let us now consider the most fascinating aspect of this patient's illness, namely, the hypocalcemia which was present at the time of admission. As you will recall, she entered the hospital with an acute febrile illness and a serum calcium of 6.2 mg. per cent; five days later she had a convulsion and then promptly went into renal failure. Dr. Daughaday, do you believe the patient actually had her convulsion on the basis of hypocalcemic tetany?

DR. WILLIAM DAUGHADAY: We have examined the record very carefully and there is a little bit of doubt about the relationship of the second serum calcium to calcium therapy. It is likely, however, that this person did have a hypocalcemic convulsion. The problem of hypocalcemic convulsions in adults is an interesting one. Convulsions as an initial or a major manifestation of hypocalcemia are very common in children and may be their only difficulty. In adults, without brain lesions, almost without exception, paraesthesias and tetanic spasms are the earliest manifestations of hypocalcemia. Convulsions can occur without tetany if the hypocalcemia is superimposed on an irritable cerebral focus.

DR. SHERRY: Dr. Levy, do we have to consider factors in this convulsion other than the hypocalcemia?

DR. LEVY: Since we are dealing with the brain in an eighty-two year old patient who had pneumonia; one can assume the brain was somewhat hypoxic. To this we can certainly add serious electrolyte changes. I think there are so many known factors here that there is an adequate explanation for the convulsion without resorting to a single space occupying focal lesion or primary pathologic disorder of the brain.

DR. DAUGHADAY: I would just like to mention

that edema of the brain may occur in prolonged hypocalcemia. Papilledema can occur as Drs. MacBride and Barr described some years ago.

DR. SHERRY: Sometimes this edema can be focal and produce focal signs. What are the causes of hypocalcemia tetany in an adult?

DR. DAUGHADAY: The major factor in maintaining blood calcium is the parathyroid hormone. Either the patient had a deficiency of parathormone, was unable to mobilize it, or could not utilize it, as occurs in pseudohypoparathyroidism. Before going on to the other possibilities let us just consider the following. Idiopathic hypoparathyroidism is a rare disease. Until 1958, there were only fifty cases reported and the oldest patient that we could find had an onset of the disease at fifty years of age, so that to consider hypoparathyroidism is a guess. In order to make the diagnosis with any confidence a concomitant hyperphosphatemia which the patient did not have would be required. Further, I am always uneasy about making the diagnosis of hypoparathyroidism in the presence of potential calcium loss. This patient had a frank history of diarrhea and so far as we can make out from the history had frequent loose bowel movements in the hospital. As tempting as the diagnosis of hypoparathyroidism would be, I would personally be against it. Now, what do we have to offer as an alternative possibility? We could postulate acute losses of calcium from the blood stream and one diagnosis we talked about in the metabolic division is unrecognized pancreatitis. However, it becomes hard to make this diagnosis in the absence of symptoms and the duration of the hypocalcemia is a little unusual. Another possibility is that she had calcium loss in her feces, and because of her osteoporosis there was a defective mobilization of bone calcium. I was rather interested in a report by Finberg* that when hypernatremia was produced in rats, it caused an acute lowering of blood calcium. Their experiments were prompted by the occurrence of hypocalcemia and hypernatremia in infants with diarrhea. We are at the opposite end of the age scale, but perhaps the mechanism would still be a contributory factor in our patient. We have no direct evidence of excessive loss of calcium. The clinical picture of the bone is not suggestive of osteomalacia, but more sug-

* FINBERG, L. Experimental studies of the mechanisms producing hypocalcemia in hypernatremic states. *Journal of Clinical Invest.*, 36: 434, 1957.

gestive of osteoporosis and this supposition is supported by the normal alkaline phosphatase. Considering all probabilities, I would suspect that she had losses of calcium in the gastrointestinal tract, probably acute and chronic, with osteoporosis which led to defective mobilization of calcium.

DR. SHERRY: Can adult tetany result from renal losses of calcium?

DR. DAUGHADAY: Tetany can rarely occur from renal losses of calcium. The metabolic response to a chronic but small loss of calcium is the development of secondary hyperparathyroidism so that the serum calcium is maintained at the expense of the bones. You get a low serum phosphorus and a normal or slightly low calcium. However, we have seen some patients with extensive calcium loss, as in sprue, in whom it was quite likely that there was a relative hypoparathyroidism. This has been reported by other investigators in the literature.

DR. SHERRY: Thus, most of the adult hypocalcemic situations occur as a result of either hypoparathyroidism *per se*, losses of calcium either through the gut or the kidney, or by sequestration such as in pancreatitis. Although tetany usually does not result in most patients with these abnormalities, a poor parathyroid response to the calcium loss sensitizes these persons to the development of frank tetany.

DR. DAUGHADAY: Occasionally in human subjects, but much more commonly in cows, hypocalcemia is a result of lactation.

DR. SHERRY: Dr. Drake, you probably have had as much experience with idiopathic hypoparathyroidism as anyone in the world. What do you think of the possibility of idiopathic hypoparathyroidism in this patient?

DR. TRUMAN DRAKE: I would agree with Dr. Daughaday that this diagnosis is not very likely, here. The triad required for the diagnosis of hypoparathyroidism is not present. We do not know what the urinary calcium is, either by qualitative or quantitative measures. We do not know what a renal biopsy would show. There are so many other complicating factors here that it would not be necessary to postulate idiopathic hypoparathyroidism.

DR. SHERRY: Since idiopathic hypoparathyroidism has never been described as having its onset so late in life, I believe we can exclude this diagnosis from further consideration. Dr. Bricker, can we also exclude renal wasting of calcium as the explanation for the hypocalcemia?

DR. NEAL BRICKER: I think it is unlikely that the patient had renal tubular acidosis or the Fanconi syndrome, in that we have no supporting data for either of these diagnoses. It also seems unlikely that she had idiopathic hypercalciuria. In any event, hypercalciuria would not have persisted during the period of time she had acute renal failure even if it had been present initially.

DR. SHERRY: Dr. Reiss, do you agree with Dr. Daughaday's final interpretation that the hypocalcemia was due to gastrointestinal losses and a poor parathyroid response, or do you think that there is another mechanism responsible?

DR. ERIC REISS: I would like to point out that only the first two calcium and phosphorus values are disturbing. Subsequently, the data are readily explained by the development of renal insufficiency and the therapy that was given.

DR. SHERRY: If only the initial hypocalcemia is obscure and renal insufficiency explains the subsequent low levels, then how do we explain the hypercalcemia which developed later?

DR. REISS: When I first saw this protocol I was suspicious of a series of laboratory errors. However, a review of the protocol and the chart made it clear that therapy influenced the later values of calcium and phosphorus. For example, the administration of parathyroid hormone was begun on December 19. The dosage used was 100 units six times a day. Six hundred units a day is quite sufficient to produce a picture of hypercalcemia and hypophosphatemia, both of which developed. Additional doses of parathyroid hormone were given subsequently. Starting on December 29, vitamin D was added to the regimen at a dosage of 20,000 units a day; this again introduces still another variable. I believe that the crucial problem is one of deciding what caused the renal insufficiency.

DR. SHERRY: Dr. Shatz, we are left with the suggestion that this patient had some chronic calcium loss from her bowel on the basis of some gastrointestinal disease. Can you suggest a gastrointestinal disease which might satisfy us?

DR. BURTON SHATZ: There is little evidence for malabsorption other than the low serum calcium and diarrhea.

DR. SHERRY: She did have a prothrombin of 48 per cent at one point.

DR. SHATZ: Right. Several features in this patient suggestive of malabsorption can be picked out: diarrhea for a long period of time, one prothrombin of 48 per cent, fractures of

bones coupled with low serum calcium, and a beefy red tongue on the second admission. However, features against the diagnosis of malabsorption are the following: stools were negative for fat; the blood proteins were normal; and the blood pressure was a little on the high side which, for some reason, is unusual in states of malabsorption. More than 30 per cent of these patients have systolic pressures lower than 100 mm. Hg. In a series of 124 patients with sprue and malabsorption, only 5 per cent had systolic blood pressures over 150 mm. Hg. However, the statement in the protocol referring to the absence of fat in stools probably means that the stools were examined microscopically and no fat globules were seen or were stainable. We know that about 20 per cent of patients with steatorrhea will have no microscopically visible fat.

Now, if this patient does have malabsorption, the possibilities can be grouped into two categories. First, those in which there is disease in the small intestinal wall, for example: sprue, Whipple's disease, metastatic or primary neoplasm, diffuse inflammatory disease, or diffuse vascular disease of the small bowel. Second, those pathologic disorders due to some pancreatic exocrine function deficiency. In this patient the only features in favor of a pancreatic disturbance were the mild diabetes, and possibly the hypocalcemia, but there was nothing else that went along with it. So, that if we are going to say this patient had a malabsorption syndrome, I would favor some primary disease of the small bowel.

DR. SHERRY: What about the possibility of a regional ileitis? This disease can be very insidious in its nature.

DR. SHATZ: Regional ileitis? I did not consider that possibility. However, regional ileitis in a woman this age which had been going on for so long with malabsorption as the only evidence of this disease would be very rare.

DR. SHERRY: Does the history of arthralgia help us?

DR. SHATZ: That, I think, would be more in keeping with Whipple's disease.

DR. SHERRY: Is not Whipple's disease seen more often in males?

DR. SHATZ: Eighty per cent males, twenty per cent females.

DR. SHERRY: Does not the absence of wasting or lymphadenopathy also mitigate against Whipple's disease?

DR. SHATZ: Right. I agree that there is not a

good case for any single primary anatomical disease of the gastrointestinal tract.

DR. REISS: Although all of us agree that this woman probably did not have hypoparathyroidism, it might be worth pointing out that three diseases are commonly associated with one another: idiopathic hypoparathyroidism, sprue, and Addison's disease. This combination of problems occurs primarily in young people. It might just be worth mentioning that one possible explanation for the association of two of these diseases is that patients may begin with sprue and then secondary hyperparathyroidism will develop as well as a tendency to bleed due to malabsorption of vitamin K. Hemorrhage in patients with hyperplastic parathyroids would then result in parathyroid deficiency.

DR. SHERRY: Dr. Shatz, do you or do you not believe this patient had a malabsorption syndrome?

DR. SHATZ: I do not.

DR. SHERRY: What about pancreatitis? Can this disease be so masked that a person might have an acute pancreatitis with marked sequestration of calcium yet not show any abdominal findings or shock?

DR. SHATZ: I would say no. In patients in whom hypocalcemia with acute pancreatitis develops there is severe pancreatitis and the diagnosis is usually fairly obvious. I think there is one other possibility that we ought to mention. The patient had a carcinoma of the breast in 1945 and although this is a long time, we know that metastatic lesions of carcinoma of the breast may show up many years after the primary lesion has been removed.

DR. SHERRY: It is of interest that a patient has been described with extensive metastases to the parathyroids from a carcinoma of the breast, but in this instance hypoparathyroidism was not present.

DR. SHERRY: Dr. Bricker, can you give us an adequate explanation for her renal failure?

DR. BRICKER: I think that we can put a number of possibly related facts together in the following way: the renal failure had its onset after the patient was admitted to the hospital. It was characterized initially by oliguria and thereafter by a period of progressively increasing urine volumes; and during the early phases of oliguria and polyuria her non-protein nitrogen continued to rise. Subsequently, both the urine volume and non-protein nitrogen decreased and ultimately the latter returned to its base line level.

On the basis of its natural history then, it is fair to define this syndrome as acute renal failure; perhaps the most common cause of this particular sequence of events in an aged, debilitated woman, with an intercurrent infectious disease, marked extrarenal losses of body fluids, and a labile blood pressure which have led to undetected bouts of hypotension, was acute tubular necrosis. Unfortunately, we know very little about her urine sediment and essentially nothing about the composition of her urine. It would be helpful to know the urinary osmolality or specific gravity, the urinary sodium concentration, the creatinine U/P ratios, etc. In the absence of at least some of these data I do not think we can document this diagnosis, but certainly on statistical grounds it would be the most likely one. One or two facts about her renal function merit comment. The patient had hypernatremia on admission. In a person with a contracted extracellular fluid volume, hypernatremia implies that the loss of water was out of proportion to the loss of sodium. Perusal of her chart indicates that her urine was hypotonic at the time that her plasma was markedly hypertonic. This then raises the following two possibilities: (1) that her thirst mechanism was defective; and (2) that her renal ability to conserve water was impaired. The causes of the latter disorder in this patient might include potassium depletion and hypercalcemia; hypercalcemia can probably be excluded on the basis of the initial low calcium value, although the rapidity of induction of hypercalcemia in association with the administration of parathyroid hormone might make one wonder whether or not there might not have been elevated blood calcium levels before admission.

DR. SHERRY: It is well recognized that hypercalcemia can cause acute renal dysfunction. Can hypocalcemia also produce renal dysfunction?

DR. BRICKER: Not to my knowledge, Dr. Sherry. However, I might add one other point. It has recently been suggested that both hypercalcemia and potassium depletion may be associated with primary disturbances of the thirst mechanism as well as the renal concentrating mechanism. At least in the case of hypercalcemia the evidence seems reasonable that polydipsia may be in part independent of the concentration defect. Thus a marked mental depression must have been an accompanying factor, if her hypernatremia is to be explained on the basis of potassium depletion. She was an eighty-two year

old woman, and statistically there is a good likelihood of some foci of pyelonephritis as well as widespread nephrosclerosis.

DR. SHERRY: Dr. Reichlin, everyone here seems perfectly confident that the hypernatremia and hyperchloremia can be explained on dehydration and alterations in the thirst mechanism. Is this the usual explanation for the hypernatremia which may be seen in diseases of the central nervous system?

DR. SEYMOUR REICHLIN: I think that is right. Whenever electrolyte abnormalities are encountered in an unconscious or stuporous patient, the tendency has been to attribute the change to some direct effect of the brain on the metabolism of electrolytes. With very few exceptions, and those are questionable, the patients that have been studied carefully indicate that the so-called cerebral hypernatremia syndromes are due to dehydration developing either because sensations of thirst are disturbed by destruction of specific "thirst centers" or because the comatose person does not consume enough water to replace fluid loss. Increased sodium retention in this setting is best explained by secondary changes in aldosterone secretion in response to contraction of the extracellular fluid volume. Although dehydration is the most common cause of "cerebral hypernatremia" it is worth mentioning that central regulation of the metabolism of electrolytes is well established. In addition to the well known functions of the neurohypophysis, there is good evidence for diencephalic influences on aldosterone secretion through release of a material termed by Farrell "glomerulotropin." Since the brain influences so many endocrine functions, one might wonder whether or not the changes in blood calcium in this case were due to disturbances of the central nervous system. Little is known about this problem; in my own experiments massive lesions of the hypothalamus in rats fail to influence plasma levels of calcium, phosphorus, or alkaline phosphatase.

DR. SHERRY: Dr. Kipnis, we were all concerned with the high carbon dioxide which developed late in this patient's course. Do you believe this was on the basis of a respiratory acidosis or a metabolic alkalosis?

DR. KIPNIS: When we reviewed the protocol, it was noted that tube feedings were started on December 19 at which time the carbon dioxide was about 20 mEq. per L. These feedings contained 50 gm. of calcium lactate which was given

per day for about ten days and then dropped to 25 gm. of calcium lactate. By the twelfth day of tube feeding, the carbon dioxide was recorded as 31 mEq. per L. and then leveled off between 35 and 38 mEq. per L. I would be inclined to think this really represented a metabolic alkalosis. However, this patient was semistuporous for the last three weeks of her hospitalization and it is possible that she failed to ventilate well. This could have led to respiratory acidosis. When the urinary pH's were checked, and I recognized the unreliability of urinary pH, they were routinely recorded as very acid.

DR. SHERRY: Then you would suggest that the patient had a combination of a metabolic alkalosis and a respiratory acidosis. Would you agree with this, Dr. Nelson?

DR. J. ROGER NELSON: Yes, I think so. She had no evidence of significant underlying chronic pulmonary pathologic disorder which would account for the high carbon dioxide. Emphysema was present which was senile emphysema; she had a good change in lung volume from the inspiratory to the expiratory chest film, which is a good rough test of residual volume. This must have been the result of acute pulmonary insufficiency plus a metabolic alkalosis.

DR. SHERRY: It is of interest that, though initially her tetany probably was due to hypocalcemia, and in the latter phases of her illness a good part of her supposed tetany could have been on a basis of an alkalosis rather than on a basis of hypocalcemia.

DR. KIPNIS: I would like to ask Dr. Bricker a question. The patient was admitted apparently dehydrated clinically, with a marked hypernatremia, and hyperchloremia with a potassium of 3.4 mEq. per L. The urine specific gravities routinely were around 1.010. I wonder if she may not have had chronic potassium depletion with some hypokalemic nephropathy.

DR. BRICKER: I think this is an excellent possibility. Did she get potassium supplementation with her high doses of calcium lactate? I just want to add one last clause and that is that it seems reasonable that the patient was potassium depleted on admission. Moreover, with all of the lactate she received during the last part of her hospital course, if supplementary potassium was not administered, she should have been profoundly potassium depleted at death.

DR. SHERRY: It will be interesting to see whether or not autopsy revealed the renal

cytologic changes seen in severe potassium depletion. Dr. Levy, would you interpret the final neurological events for us and tell us what you think they were due to.

DR. LEVY: If this final examination of a stuporous eighty-two year old woman is to be believed, that is the anesthesia and lack of withdrawal of the right arm on stimulation, then one might suppose that she had some terminal infarction. This is not too clear because such an examination would be rather difficult.

DR. SHERRY: Since her blood pressure fell before these neurological findings developed, would you attribute this picture to infarction of the brain or of the myocardium?

DR. LEVY: As a matter of fact it could be in association with either, because a myocardial infarct can precipitate brain changes either of infarction or of oxygen insufficiency.

DR. SHERRY: And, you doubt the existence of any serious underlying disease other than chronic cerebral arteriosclerosis perhaps with a terminal thrombosis and infarction?

DR. LEVY: That is correct.

DR. SHERRY: We may offer as our final clinical diagnosis: severe hypocalcemia and tetany probably secondary to some gastrointestinal disease such as a malabsorption syndrome, with regional enteritis or a masked pancreatitis as less likely possibilities; chronic bronchitis and pulmonary emphysema; possible Friedländer's pneumonia, recovered; generalized and cerebral arteriosclerosis with chronic brain syndrome; healing acute tubular necrosis perhaps with evidences of a superimposed hypokalemic nephropathy; and a terminal cerebrovascular accident or unsuspected myocardial infarction.

PATHOLOGIC DISCUSSION

DR. R. M. O'NEAL: At autopsy the patient appeared moderately obese and had the surgical scars of a left simple mastectomy, hysterectomy and cholecystectomy. A small decubital ulcer was present over the right greater trochanter. Only inconsequential amounts of fluid were present in the serous cavities. Atherosclerosis was moderately advanced in all major arteries, but appreciable narrowing was present in none. The brain was rather atrophic, especially the frontal lobes, and weighed 1,150 gm. but no localized lesions were present. No evidence of an active infectious process was found in any organ, and

our postmortem culture of blood was sterile. The gastrointestinal tract was completely normal, except for focal areas of congestion in the cecum and the ileum. The heart was large, weighing 420 gm. The degree of osteoporosis was not great, appearing of the degree usually found in an eighty-two year old woman. The parathyroids were microscopically perfectly normal, compatible with the patient's age.

Surprisingly, residual carcinoma was present in this patient with a ten year "cure" following simple removal of a carcinoma of the breast. Metastatic foci in the lungs and mediastinal lymph nodes were very widely spaced and small. It is unlikely that this cancer had anything to do with her death, although it obviously did contribute somewhat to the extent of pulmonary parenchymal involvement by various processes, which will be shown later.

The adrenals were relatively normal, with only slight depletion of fat. One healed focal area of necrosis was present, but this appears to be unrelated to other pathologic processes. Numerous fat-filled macrophages replaced the cortex in the area of necrosis.

Multiple small foci of recent fat necrosis were found in the head of the pancreas. (Fig. 2.) Some were filled with fat-laden macrophages. Very little calcium deposition (basophilic granular material) was seen, but some foci had hazy blue borders, and this calcium accumulation possibly could account for some of the hypocalcemia. We see this degree of focal fat necrosis fairly commonly in autopsy and, as far as I am aware, it is usually unassociated with significant hypocalcemia. To repeat, the pancreatic fat necrosis was focal, definitely not extensive and I know of no way of estimating how much calcium uptake could have occurred in these areas.

Patchy small areas of fibrosis were found throughout both lungs. This was much more prominent at autopsy than it was radiologically. Microscopically, solid sheets of fibrous tissue surrounded air spaces which appeared to be atria with prominent epithelium. (Fig. 3.) However, this occupied a rather small part of the total lung volume and in other areas there was relatively normal parenchyma with moderate "senile" emphysema. The smaller bronchi were dilated throughout most of the lungs and there was a great deal of mucus production, with mucus plugs in many. The bronchiectasis of smaller bronchi, patchy fibrosis and senile emphysema formed a background of chronic

pulmonary disease on which the clinical episode of pneumonia was superimposed, but the functional impairment produced by such chronic disease is notoriously difficult to evaluate pathologically.

Some evidence of a recently active pneumonic process was evident. Fibrous tissue proliferation into remaining air spaces was occurring at scattered points, quite consistent with healing, organizing klebsiella pneumonia. (Fig. 4.)

The kidneys were markedly affected by arteriolar nephrosclerosis; they were rather small, both weighing only 230 gm. They had very granular surfaces, but no scarring characteristic of pyelonephritis. Microscopically, hyaline changes were moderately advanced in arteriolar walls but the glomeruli showed little scarring. The most remarkable change was swelling of the cytoplasm of the epithelial cells of proximal convoluted tubules which affected approximately one-fourth of these tubules to some degree. Their cytoplasm was filled with large and small vacuoles. The collecting and distal convoluted tubules were not affected. (Fig. 5.) Parrish, Rubenstein and Howe* described three patients with pneumonia and a history of high intake of alcohol who had uremia; a renal biopsy was obtained in one patient during the period of azotemia which showed vacuolization of renal tubules. This lesion persisted on repeated biopsy specimens, even after functional renal impairment disappeared. The lesion was similar to that in the patient discussed today, and may, therefore, be of similar origin. However, vacuolar tubular change is obviously not pathognomonic of any single metabolic disturbance. In our patient, the relationship of the vacuolar change to the uremic episode, as well as the underlying cause of both, remains unclear.

The final anatomical diagnoses were: widespread, focal chronic pneumonia with organization and fibrosis in all lobes of the lungs (history of Friedländer's pneumonia for one and a half months); emphysema of the lungs, moderately advanced; vacuolization of the epithelium of the renal proximal convoluted tubules, moderate; left mastectomy scar (history of radical mastectomy for carcinoma of the left breast) with metastases in the lungs and tracheobronchial and paraesophageal lymph nodes; chronic

* PARRISH, A. E., RUBENSTEIN, N. H. and HOWE, J. S. Acute renal insufficiency associated with respiratory infections. *Am. J. Med.*, 18: 237, 1955.

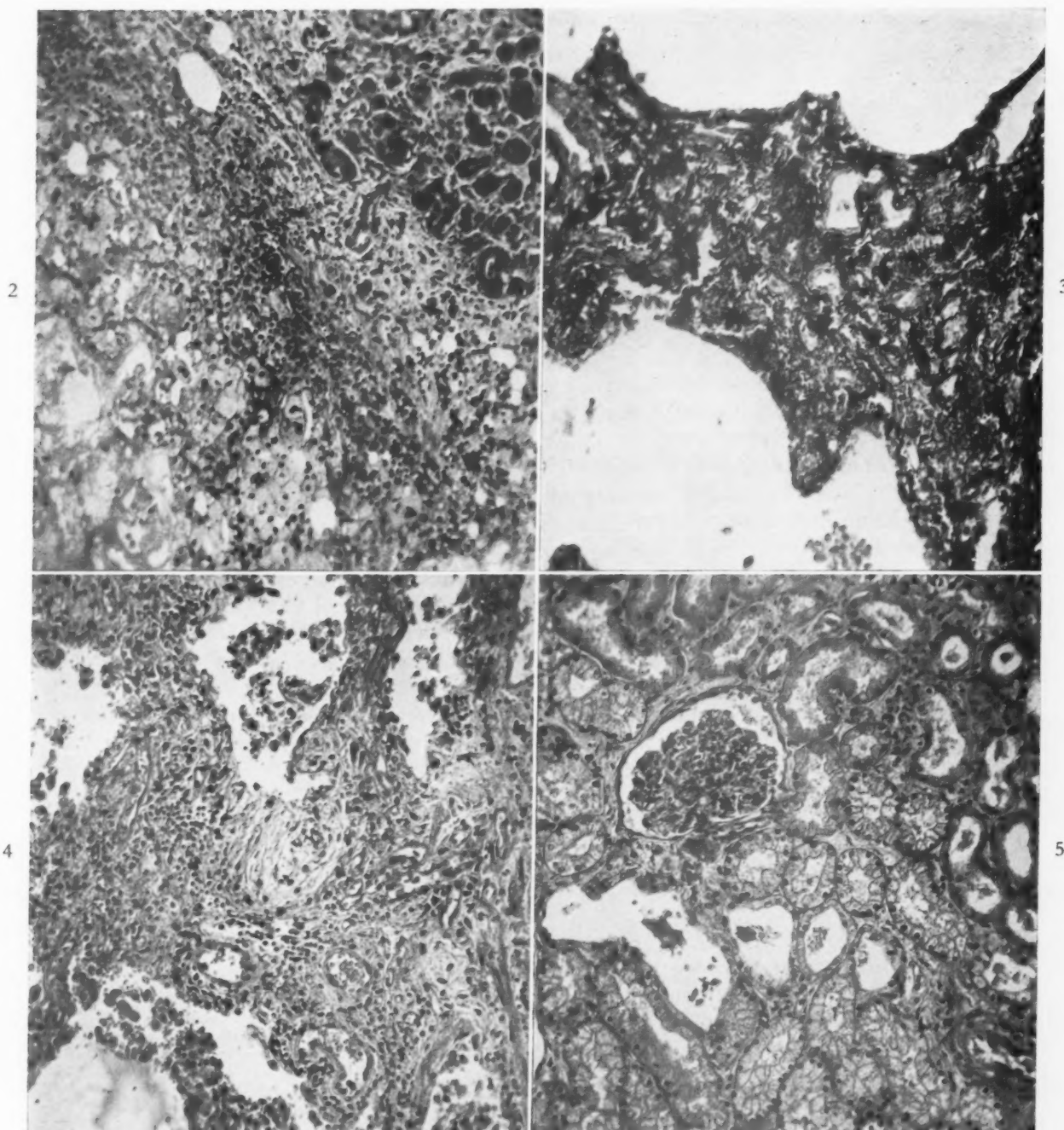


FIG. 2. The edge of a focal area of fat necrosis in the pancreas. Acinar tissue is present at the upper right, the necrotic fat at lower left. No visible calcium deposits are present, but a moderate cellular infiltrate borders the necrotic area. Hematoxylin and eosin, $\times 100$.

FIG. 3. A thick, fibrotic area of the lung between two atria, probably the results of obliterative collapse of alveoli. Focal areas of such change produced the gross picture of focal fibrosis. Elastic tissue, appearing black, is coarse and fragmented. Aldehyde fuchsin—van Gieson—hematoxylin, $\times 100$.

FIG. 4. Another focus with pulmonary fibrosis extending between large air spaces. In the center is a lighter area that represents actively proliferating fibrous tissue protruding into an air space. Such a focus is characteristic of organization of intra-alveolar exudate, probably following the recent pneumonia. Hematoxylin and eosin, $\times 100$.

FIG. 5. Renal proximal convoluted tubules in the lower two-thirds of this field are swollen and vacuolated. Approximately one-fourth of all the proximal tubules were affected in this manner. The distal tubules are dilated but their epithelium is intact. Proximal tubules at upper left appear normal. Hematoxylin and eosin, $\times 100$.

pancreatitis, focal, with fibrosis and interstitial inflammation; focal pancreatic fat necrosis.

The accessory diagnoses were: arteriolar nephrosclerosis, moderate; hypertrophy of the left ventricle of the heart (heart weight 420 gm.); arteriosclerosis of the abdominal aorta, advanced, and of the thoracic aorta, renal, coronary, cerebral and splenic arteries, moderate; sclerosis of the bases of the cusps of the aortic and of the anterior leaflet of the mitral valves; fibrous pleural adhesions over the posterior aspects of the upper and lower lobes of the left lung and over the apex of the right lung; granulomas in the liver, few, small; localized scar of the adrenal cortex; suprapubic abdominal scar with absence of the body of the uterus, ovaries, oviducts and appendix (history of operation for chronic salpingitis and endometritis, about twenty years previously); scar in the right upper quadrant of the abdomen with absence of the gall bladder (history of cholecystectomy for chronic cholecystitis, about fifteen years previously); dilatation of the extrahepatic bile ducts, including a large remnant of the cystic duct.

DISCUSSION

DR. SHERRY: It appears to me that these renal changes are characteristic of the hypo-

kalemic nephropathy described by Relman and Schwartz.

DR. REISS: We get little explanation of the renal failure from the pathologic disorder. I would like to ask Dr. Bricker whether or not a hypokalemic nephropathy could account for the course of her renal failure as we saw it here.

DR. BRICKER: No. But the fact that no definitive evidence of acute tubular necrosis was found at autopsy does not exclude this diagnosis, for she died some time after she recovered from acute renal failure. Certainly the hypokalemic nephropathy, which I am firmly convinced existed from these slides, could have contributed to her inability to conserve water and perhaps to her hypernatremia.

DR. SHERRY: Although Dr. O'Neal has not attached much significance to the pancreatitis in this case, the pancreas was the seat of multiple, although focal, areas of fat necrosis and some of these foci contain calcium deposits. Since onset of the pancreatic lesions appears to be consistent with the time of the patient's final admission, the occurrence of a pancreatitis in a febrile debilitated elderly person, presumably with a poor parathyroid response, seems to offer the most reasonable explanation for the hypocalcemia seen early in her course.

Case Report

Pulmonary Alveolar Proteinosis with Unusual Complicating Infections*

A Report of Two Cases

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IN 1958 Rosen, Castleman and Liebow [1] reported twenty-seven cases of a new chronic lung disease under the designation "pulmonary alveolar proteinosis." Since then additional cases have been described [2-7]. The microscopic features of the disease described by Rosen, Castleman and Liebow [1] were specific and surprisingly consistent in all cases. The clinical features varied; the predominant symptoms in their twenty-seven patients were either those of chronic respiratory insufficiency or of recurrent episodes of acute pneumonitis. Increasing pulmonary dysfunction was apparently the cause of death in eight cases [1]. Fungal infections frequently complicate the disease [1,4]. Radiologically the disease was characterized mainly by a feathery perihilar density in a "butterfly" distribution, although paradoxically the symptomatology and auscultatory findings were minimal. With the exception of one patient in whom the disease showed definite clinical improvement following the administration of prednisone [3], adrenocorticoids or antibiotics apparently did not alter the course of the disease in most cases [1]. Potassium iodide in large doses was followed by clinical improvement in one case [7].

The etiology of the disease is not known. A resemblance to *Pneumocystis carinii* has been noted [1,6] but no organisms were demonstrated. Further, pneumocystis occurs chiefly in infants [8] while alveolar proteinosis appears to be a disease of adults predominantly occurring in men [1]. In many of the cases there was occupational exposure to respiratory irritants. Geographical and racial boundaries of the disease are extended

by the report of a case occurring in a Chinese male living in New Zealand [7].

The present report presents clinical and pathological findings of two additional cases of pulmonary alveolar proteinosis, with further characterization of the alveolar lesion.

CASE REPORTS

CASE I. In July 1951 the patient a twenty-six year old white woman from eastern Kansas injured her left knee. Because of the possibility of tuberculous arthritis and a positive reaction to the tuberculin skin test with a strong family history of tuberculosis, she was admitted to the State Sanitarium for Tuberculosis. Once in 1949 and twice in 1950 she reported having had "pneumonia."

On admission she appeared pale and emaciated, and complained of fatigue, weakness, anorexia, fever, night sweats and weight loss. Except for a hypochromic anemia, the roentgenographic and the laboratory investigations, including many for infectious diseases, revealed no abnormalities. Although no acid-fast bacilli were isolated from sputums and fluid from the knee, she was given dihydrostreptomycin, 1 gm. daily, along with supportive therapy. She had a low grade fever during the first month of her three-month period of hospitalization. After discharge, she continued to feel weak and was unable to gain weight. In April 1953 another episode of pneumonia apparently developed. A few months later surgical repair of a draining rectal fistula was performed at the University of Kansas Medical Center. A roentgenogram of the chest at that time showed bilateral, patchy infiltration in the infraclavicular and perihilar lung fields (Fig. 1A), thought to be fibrotic in nature.

In October, 1955 she was readmitted to the State Sanitarium because of a cough, blood-streaked

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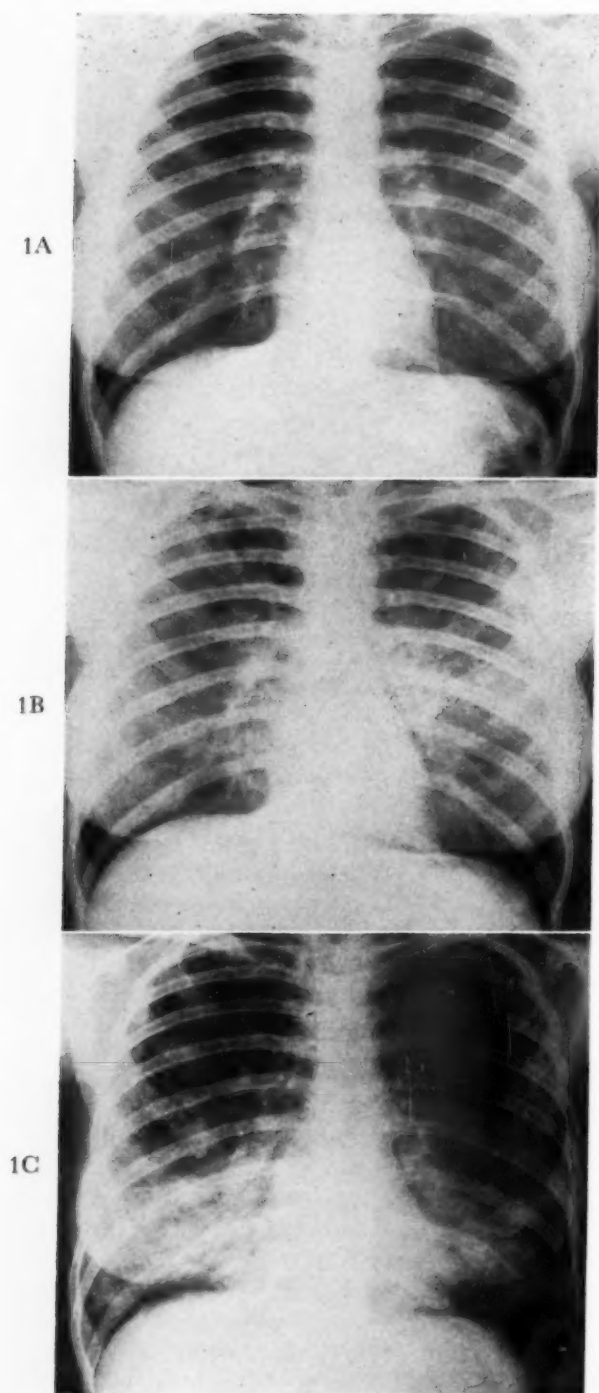


FIG. 1. Case 1. A, roentgenogram of the chest taken on October 5, 1953. There is a patchy infiltrative type of lesion in the peripheral lung fields in each infraclavicular area at the first and second interspaces bilaterally. The changes appear fibrotic in nature. B, roentgenogram of the chest taken on January 2, 1956. A diffuse fine reticular type of lesion is distributed throughout the lungs on both sides, with a diffuse pneumonitis in the upper half of the right upper lobe. C, roentgenogram of the chest taken on July 12, 1958. A diffuse hard fibrosis extending from the apex to the diaphragm on both sides is suggested. In the basal regions this appears to have a somewhat nodular character.

sputum, chest pain and weight loss. Roentgenograms of the chest showed a fine reticular pattern in the lungs. (Fig. 1B.) While the results of the histoplasmin skin test was now positive, the complement fixation test for histoplasmosis was negative. Attempts to isolate acid-fast bacilli and fungi were unsuccessful, and only *Staphylococcus albus* and non-hemolytic streptococcus were cultured from bronchial aspirates. The patient was started on a regimen of dihydrostreptomycin and isonicotinic acid hydrazide; later penicillin and tetracycline were added. Blood transfusions were given for anemia. She left the hospital on March 19, 1956, against advice. On April 17, 1957, she required rehospitalization for seven days after the gradual return of symptoms. At this time the hemoglobin was 6.8 gm. per 100 ml. The white blood cell count was not elevated, but the differential showed a shift to the left and a moderate lymphocytosis. She was given sulfisoxazole and streptomycin, after which the temperature fell to normal from a high of 104°F. Again no acid-fast organisms were isolated from the sputum or gastric washings. Some months later (December 1957) she again contracted "pneumonia."

She was hospitalized on April 28, 1958, for sudden, severe abdominal pain, and a "hemorrhagic ovarian cyst" was found at laparotomy. She was anemic, the white blood cell count was 1,800 per cu. mm. with 72 per cent lymphocytes. Bone marrow studies were suggestive of leukemia or of metastatic malignancy.

She was last admitted to the University of Kansas Medical Center on June 11, 1958, with complaints of constant, severe, throbbing headaches, loss of appetite with nausea, exertional dyspnea and pedal edema. The blood pressure was 90/55 mm. Hg; pulse 100 per minute; respiratory rate 24 per minute. The following features were noted: emaciation; marked pallor of the skin, and clubbing of the fingers; right sided scotoma, and ptosis of the left eyelid; venous congestion of the retinas with numerous flame-shaped hemorrhages and exudates; focal ulcerations of the buccal mucosa; scant rales over both lung fields; and a grade 2, apical systolic murmur with a slightly accentuated pulmonary second sound.

Laboratory data were as follows: hemoglobin 5.6 gm. per 100 ml.; hematocrit 16.5 volume per cent; white cell count 2,000 per cu. mm. with nineteen neutrophils of which twelve were non-filamented, fifty-five lymphocytes, one metamyelocyte, one myelocyte, one plasma cell, twenty-two bizarre blast cells, one nucleated red cell and a rare megakaryocyte per 100 white cells; platelet count 334,000 per cu. mm. with many giant forms present; sedimentation rate 40 mm. in one hour; reticulocyte count 0.7 per cent; total blood protein 7.3 gm. per 100 ml. with 3 gm. of albumin and 4.3 gm. of globulin; fasting blood sugar 106 mg. per 100 ml. The spinal fluid contained 2 red cells per cu. mm., with 77 mg. of glucose and 24 mg. of protein per 100 ml., and gave a negative reaction to the Wassermann test. Cultures of the spinal fluid were

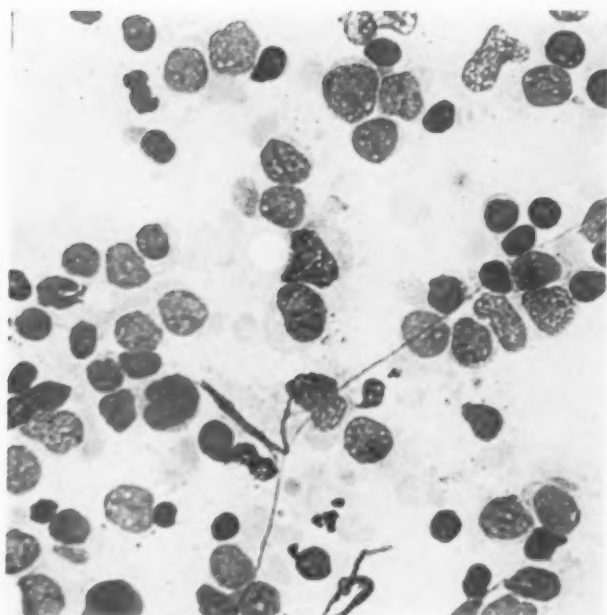


FIG. 2. Case 1. Bone marrow smear taken on June 17, 1958. There are immature mononuclear cells at the blast stage, immature myelocytes and immature megakaryocytes. Wright's stain, magnification $\times 550$.

negative for *Mycobacterium tuberculosis*. *Candida albicans*, *Aerobacter aerogenes*, *Streptococcus viridans* and *neisseria* species were cultured from the sputum which also showed many mycelia of *candida* species on smears.

Roentgenograms of the chest suggested a diffuse fibrosis of both lung fields extending from the apex to the diaphragm, and of nodular character at the bases. (Fig. 1C.) There was no hilar adenopathy. Repeat roentgenographic examinations were unchanged.

The clinical impression was acute leukemia. Bone marrow aspirates were difficult to interpret. (Fig. 2.) Immature mononuclear cells at the blast stage appeared in clusters and sheets with normal elements of the erythroid and myeloid series scattered throughout. Many immature megakaryocytes and abnormal platelets, many of the giant variety were present. Transitional forms between the blast cells and the immature megakaryocytes were identified. The patient was started on a regimen of 150 mg. of 6-mercaptopurine, 40 mg. of prednisone and 300 mg. of isonicotinic acid hydrazide orally daily. The temperature and pulse rate, which were previously elevated during the first week of admission, promptly fell to near normal values. However, seven days later the fever recurred, and she became dyspneic. Penicillin and Chloromycetin® were given. The administration of 6-mercaptopurine was discontinued because of a falling white blood count. On July 4 she became jaundiced and her liver was enlarged and tender. The serum total bilirubin was 8.1 mg. per 100 ml., with 4.7 mg. of direct acting bilirubin. The white blood cell count had fallen to 310 per cu. mm. She died three days after the appearance of jaundice.

OCTOBER 1960



FIG. 3. Case 1. Cross section of fixed lungs. There are large air cysts and fibrosis in the upper lobes and multiple pale patchy infiltrates of proteinosis.



FIG. 4. Case 1. Alveolar proteinosis of the lower lobe of the right lung.

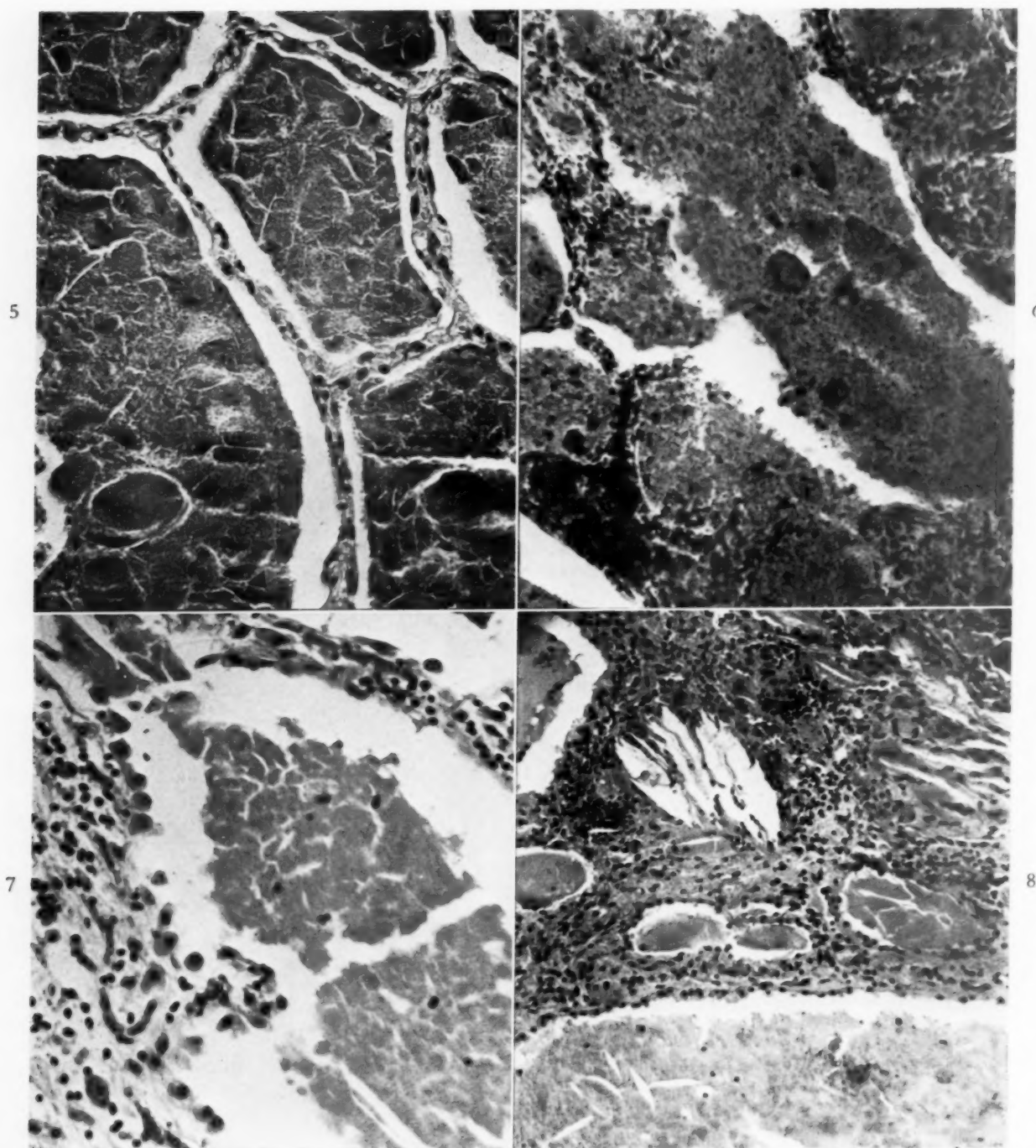


FIG. 5. Case 1. Alveolar proteinosis. Periodic acid-Schiff stain, magnification $\times 240$.

FIG. 6. Case 1. Oil Red-O stain of frozen section of proteinaceous material. There is intracellular lipid in the alveolar walls and extracellular droplets of fat in the proteinaceous material. The proteinaceous material stains diffusely and moderately. Magnification $\times 175$.

FIG. 7. Case 1. Alveolar proteinosis showing swollen and sloughing alveolar lining cells, nuclear debris and an acicular space where a crystal has been. Hematoxylin and eosin, magnification $\times 300$.

FIG. 8. Case 1. Fibrosis, lymphocytic infiltrations and giant cells in alveolar walls surrounding crystal aggregates in the lower lobe of the lung. Note the small deposits of proteinaceous material and the presence of acicular spaces in the larger deposit. Fibroblasts and giant cells appear to grow along the margins of the acicular spaces at the upper center in the picture. An alveolus almost completely organized by fibrous tissue is present at the right margin of the photograph. Hematoxylin and eosin, magnification $\times 240$.

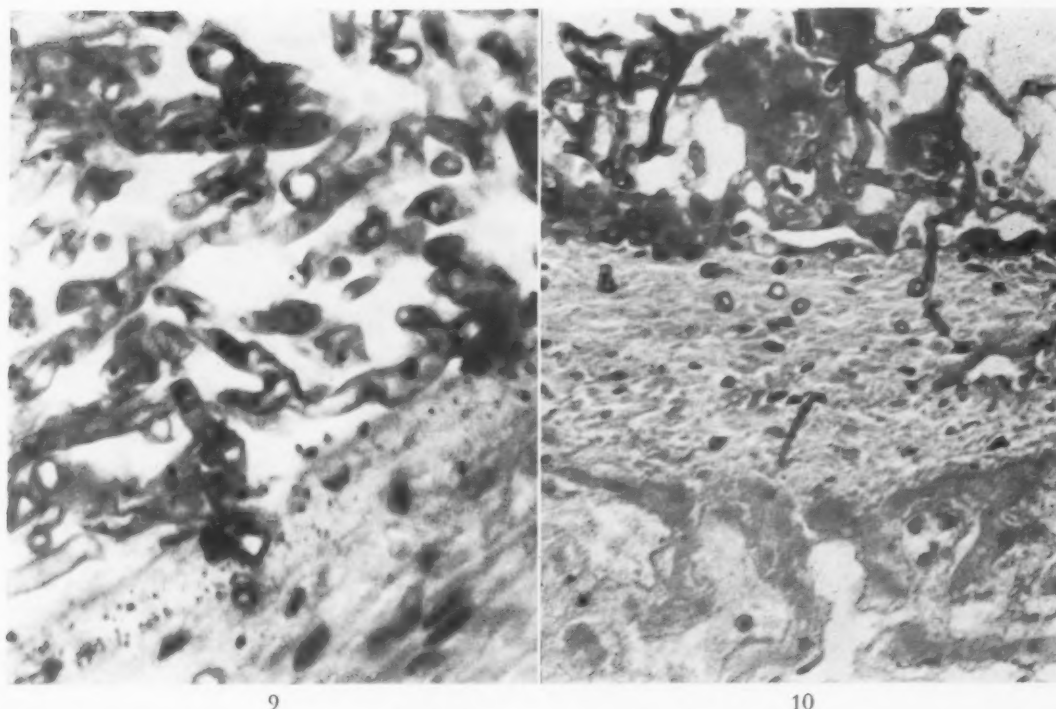


FIG. 9. Hyphae of mucormycosis filling a pulmonary artery. Periodic acid-Schiff stain, magnification $\times 550$.

FIG. 10. Mucormycosis of a fibrinous exudate overlying a liver infarct. In deeper areas (not shown) similar hyphae occlude hepatic vessels. Periodic acid-Schiff stain, magnification $\times 300$.

Autopsy (KUMC No. 2493) was performed fourteen hours after death. Significant pathological changes were found in the lungs, liver, brain, gastrointestinal tract and bone marrow.

The lungs together weighed 2,600 gm. Diffuse pleural adhesions were present. A large thrombus occluded the left pulmonary artery and its branches, and the lower lobe and the inferior portion of the upper lobe of the left lung were infarcted. The lungs were emphysematous, most markedly in both apices where large air-filled cysts imparted a honeycomb appearance. (Fig. 3.) The most striking features were firm, smooth, irregular, patchy yellowish infiltrates filling scattered groups of alveoli. These infiltrates were confluent in the extensively involved lower lobes of the lung. (Fig. 4.) The intervening parenchyma was essentially normal in appearance. Tissue blocks sank in water. The hilar and tracheobronchial lymph nodes were moderately enlarged and soft. Microscopically, there were large groups of alveoli filled with a diffusely, granular, flocculent, lightly eosinophilic, acellular material that was frequently confluent with adjacent deposits through natural channels. (Fig. 5.) This alveolar material had the following staining characteristics: (1) a positive reaction with the periodic acid-Schiff (P.A.S.) stain was obtained before and after diastase treatment of sections; (2) it stained lightly but diffusely with the oil red-O fat stain (Fig. 6); (3) a strongly positive reaction for cholesterol with the Schultz method was demonstrated; (4) meta-

chromasia was found with aqueous toluidine blue staining, although this was lost after alcoholic dehydration and; (5) luxol blue staining was strongly positive. Stains for amyloid, fibrin, iron, calcium and elastin were negative, as were the Ziehl-Nielson, Fite's and Brown-Brenn methods for microorganisms. There was no evidence of a *Pneumocystis carinii* infection. Acicular crystals were frequently seen in the alveolar material. These crystals were refractile when frozen sections in aqueous media were viewed under polarized light. The crystals were removed by dehydration through alcohols. (Figs. 7 and 8.) Desquamation and degeneration of swollen septal lining cells into the granular, floccular material was occasionally found. (Fig. 7.) These cells stained less intensely with P.A.S. stain than the alveolar material, although they were more sudanophilic. The alveolar walls between deposits of the material were usually normal in size and appearance but in many places, particularly the lower lobes of the lungs, septal and alveolar walls were thickened by fibrosis and contained scattered lymphocytes and swollen macrophages. (Fig. 8.) In addition, in the right lower lobe of the lung, alveolar walls surrounding the proteinaceous deposits that showed many crystals contained multinucleated foreign body-type giant cells and lymphocytes. Some alveoli in this situation showed fibrous obliteration.

Sections from all lobes of the lung showed the presence of a non-septate fungus. The pulmonary artery and vein of the infarcted lower left lobe of the

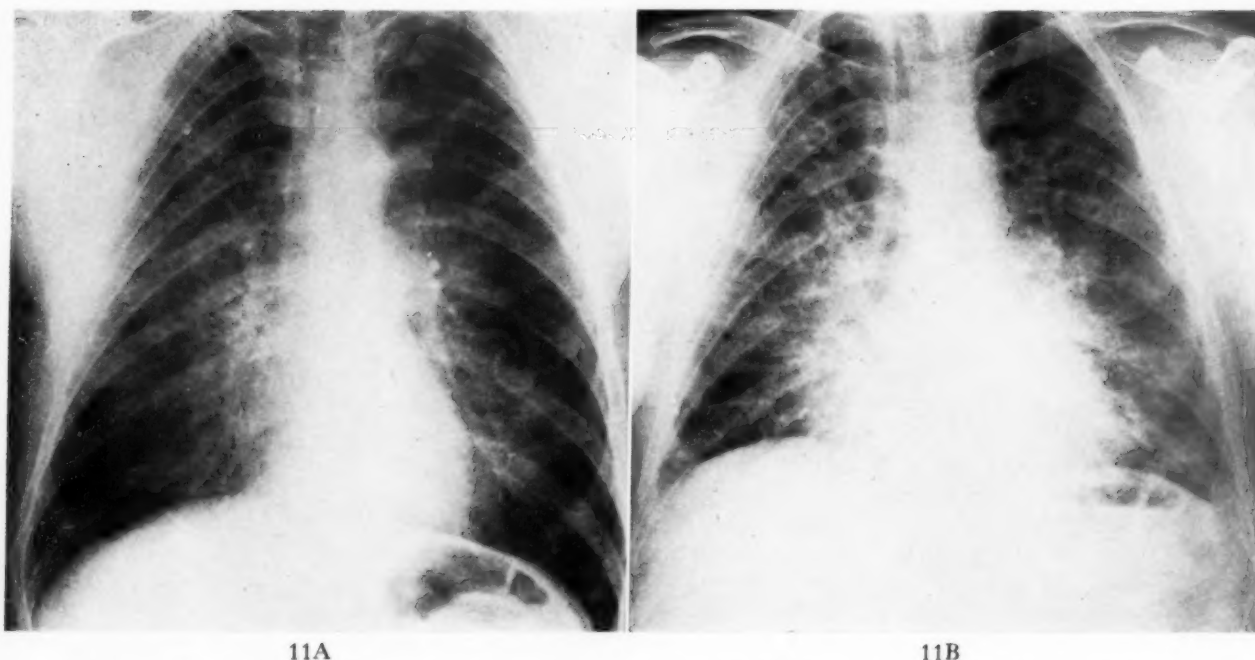


FIG. 11. Case II. A, roentgenogram of the chest taken on August 23, 1954, showing a diffuse interstitial infiltration throughout both pulmonary fields. B, roentgenogram taken on November 3, 1954, showing a perihilar infiltration with increase in radial markings throughout both lungs. The infiltration follows the course of the bronchi into the upper lobes. Patchy pneumonic consolidations are present in the bases.

lung were occluded by dense masses of broad hyphae which penetrated the vessel walls (Fig. 9), bronchiolar walls and alveolar septa. The fungus was morphologically a *Phycomycete* and its presence in the tissue represents mucormycosis [9].

The liver weighed 1,800 gm. A circular, slightly bulging, brick-red infarct measuring 7 cm. in diameter was found on the anterior surface. There was thrombotic occlusion of large portal vessels within the lesion by masses of hyphae similar to those found in the lung. The fungus extended through the vessels into the adjacent parenchyma and was also present on the peritoneal surface over the infarct. (Fig. 10.) The brain weighed 1,500 gm. There was a well defined infarct of the cortex of the posterior portion of the parietal lobes bordering both sides of the sagittal fissure. The cortical vessels in these areas were plugged with masses of similar appearing hyphae which were confined within the vessels. The right eye showed only autolytic changes.

The hypopharynx and esophagus were studded with irregular, elevated, grayish white, friable plaques that measured up to 1 cm. in diameter. There were also multiple small nodules 1 mm. in diameter scattered over the mucosa of the small bowel. Microscopically these plaques and nodules were composed of clusters of fungi exhibiting the morphological characteristics of *C. albicans*.

The marrow spaces of the ribs, sternum, vertebral bodies and femur contained very small amounts of a granular appearing fatty marrow. It was hypoplastic and the cellular pattern was similar to that described

clinically. The spleen (weight 120 gm.) showed chronic passive congestion and sections revealed slight depletion of lymphoid tissue, as did the lymph nodes. In both there were increased numbers of large macrophages and erythrophagocytosis. There was no evidence of leukemia. A Perl reaction for iron was markedly positive in the spleen and bone marrow, weakly positive in the liver, and negative in the pancreas. No acid-fast bacilli were cultured from many organs and only candida species was isolated from the lungs.

CASE II. A forty-six year old white male aircraft company employee from Wichita, Kansas, was well until the summer of 1954 when he noticed easy fatigue and somnolence. On August 14, 1954 a severe headache suddenly developed followed a few days later by a non-productive cough, mild dyspnea, chills, fever, nausea and vomiting. There was no history of exposure to, or family history of, tuberculosis or fungus diseases. On admission to the hospital there was moderate cyanosis of the lips, a grayish tint to the skin, and a slight clubbing of the phalanges. Bilateral diffuse harsh breath sounds were heard over the lung fields. The remainder of the physical examination was non-contributory. The roentgenograms of the skull were not unusual. A roentgenogram of the chest (Fig. 11A) showed diffuse interstitial infiltration throughout both pulmonary fields. There was a hemoglobin value of 18.8 gm. per cent and an increased protein level in the cerebrospinal fluid; otherwise laboratory findings revealed no abnormali-

ties. Nine days later he was febrile, nuchal rigidity developed and he became comatose. Examination of spinal fluid at this time showed 2,000 white cells per cu. mm., mostly neutrophils, and increased protein with a normal sugar value; no acid-fast bacilli or fungi were found on smear or cultures. Cortisone was given, 300 mg. daily in decreasing doses, later replaced by the administration of adrenocorticotropin (ACTH). He slowly regained consciousness and became afebrile although stiffness of the neck persisted. Acid-fast bacilli were found on three consecutive daily sputum smears, but cultures were negative. He was given 12 gm. of para-aminosalicylic acid and 300 mg. of isonicotinic acid hydrazide daily, and 2 gm. of dihydrostreptomycin every third day. One month later he became febrile, he had a non-productive cough and a pleuritic type of pain on the right side of the chest where rales were heard. Roentgenograms of the chest were unchanged but the spinal fluid white cell count was still elevated with a predominance of neutrophils.

Shortly after, on admission to the University of Kansas Medical Center on October 27, 1954, there was found, in addition, slight rigidity of all muscle groups, with generalized weakness. During the entire hospital stay (40 days) leukocytosis was present, also pyuria with slight albuminuria. Results of the tuberculin, histoplasmin, blastomycin and coccidioidin skin tests were negative as were complement fixation tests for histoplasmosis and for seven neurotropic viruses.*

Cultures of blood and urine specimens taken during a febrile period yielded proteus species; 1 gm. of chloromycetin was given every four hours. Roentgenograms of the chest showed increased radial markings in both lungs with a patchy pneumonic consolidation at the bases. (Fig. 11B.) Fine densities appeared to follow the course of the bronchi in both upper lobes of the lungs. Fever and nuchal rigidity persisted, and on November 22, 1954 examination of the spinal fluid revealed a pressure of 420 mm.; 573 cells per cu. mm. with 90 per cent neutrophils; 39 mg. per cent glucose and 170 mg. per cent protein. Smears and cultures of the spinal fluid, urine, sputum, gastric washings, including guinea pig inoculations, were negative for acid-fast bacilli as well as for fungi and bacteria. Spinal fluid cytology for malignancy was negative. The patient's condition deteriorated and he died on December 2, 1954.

Autopsy (KUMC No. 914) was performed six hours after death. The findings of chief interest were in the lungs and brain.

The lungs together weighed 1,900 gm. and the pleural surfaces were a normal light gray color. There was increased crepitation in the apices of both

* Prepared by the Department of Health, Education and Welfare, U. S. Public Health Service, Communicable Disease Center, Laboratory Branch, Virus Rickettsia Section, Montgomery, Alabama.

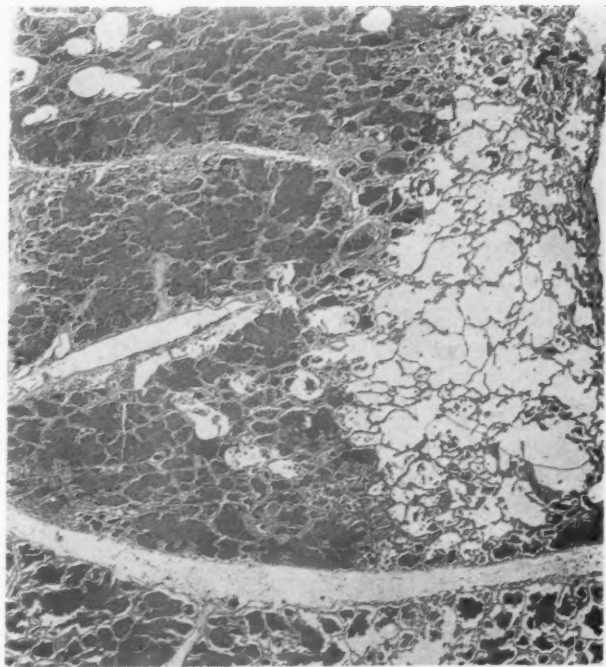


FIG. 12. Case II. Alveolar proteinosis. There is emphysema of the empty alveoli near the pleural surface. Periodic acid-Schiff stain, magnification $\times 17$.

lungs and in the middle lobe of the right lung because of multiple scattered emphysematous bullae. On cut surfaces there were multiple, irregular, homogenous, yellow, firm consolidations, chiefly peribronchial in distribution, scattered in all lobes. There was slight scarring at the apices of the lungs. No acid-fast bacilli or fungi were found in a small calcified focus present in a left hilar lymph node. Microscopically, scattered peribronchial alveoli in all lobes were filled with a finely granular and amorphous lightly eosinophilic material, some containing small acicular clefts and large foamy macrophages. (Fig. 12.) Fat stains showed an abundance of sudanophilic material within these macrophages and within the alveolar material. The alveolar walls were thin and contained a few lymphocytes. Brown-Brenn stains showed both gram-positive and gram-negative cocci within macrophages and free in alveoli. No inclusion bodies or organisms of *Pneumocystis carinii* were present. Similar results with histochemical methods used in the first patient (Case I) were obtained.

The brain weighed 1,200 gm. and showed a resolving meningitis involving principally the undersurface of the cerebellum and brain stem, and, to a lesser extent, the spinal cord. An abscess with a granulomatous component was found within the center of the left lobe of the cerebellum, with extension to cortex and the fourth ventricle. Cultures were not taken and smears failed to show acid-fast bacilli. A few long delicate gram-negative rods which contained a few gram-positive dots were found in tissue sections.

The kidneys together weighed 290 gm. A large

calculus obstructed the left ureter and the left kidney showed moderate hydronephrosis, extensive acute and chronic pyelonephritis and calcinosis. No microorganisms were identified in tissue sections. The remaining findings at autopsy revealed no abnormalities.

COMMENTS

Both patients presented typical pulmonary lesions of alveolar proteinosis. The first patient possibly had the disease over a seven-year period. The other patient had symptoms for only a few months. Both patients had dyspnea, slight cyanosis, clubbing of the phalanges, and pleuritic chest pains, both progressed to marked debilitation and died with superimposed infections.

The relationship, if any, of fungal, tuberculous and bacterial infections to alveolar proteinosis is not clear. Disseminated mucormycosis was present in Case 1 (Figs. 9 and 10) and infarcts caused by this fungus in the lungs, liver and brain were probably the direct cause of death. Mucormycosis has most often been found occurring terminally in debilitating diseases [9,10]. Besides the terminal severe debility, protracted administration of corticosteroids, antimetabolites and antibiotics has been suggested as predisposing to the frequent fungal infections in cases of alveolar proteinosis [7].

In both patients reported on herein there was a strong suspicion of tuberculosis, but this was not established clinically and no evidence was found at autopsy. At least one case of alveolar proteinosis had been preceded by proven tuberculosis [6]. In Case II the presence of severe inflammatory renal disease may indicate the source of the proteus bacteremia, which in turn may have either caused or complicated the central nervous system lesions. The gram-negative rods that were present in the cerebellar abscess could represent proteus organisms, however, no cultures were taken at autopsy. It seemed apparent, clinically at least, that the pulmonary disease preceded the bacterial infections.

The hematologic status of one patient (Case I) was difficult to establish. The persistent anemia and leukopenia during her prolonged respiratory illness and the findings at autopsy of hemosiderosis and erythrophagocytosis may have been a reflection of an acquired hemolytic anemia of unknown cause. The clinical findings during her last two months of life were not inconsistent with a diagnosis of leukemia, but this could not be established at autopsy. The clinical (Fig. 2)

and postmortem bone marrow findings might in part reflect bone marrow exhaustion, or a response to the chronic pulmonary infection, or both. This case is somewhat similar to that of a young woman confirmed as having alveolar proteinosis with marked thrombocytopenia [5,6]. In both cases an abnormal megakaryocytic and platelet response occurred terminally. Those investigators speculated that the destruction of very large numbers of platelets in the lung led to deposition of the "intra-alveolar coagulum" [6]. Except for mild polycythemia in a few instances none of the other cases of alveolar proteinosis so far reported showed hematologic abnormalities.

The studies of Rosen, Castleman and Liebow [7] indicated that the proteinaceous material in the alveoli was predominantly a mucoprotein and not a lipoprotein. However, the proteinaceous material in our patients did contain a very large amount of lipid as indicated by fat stains. (Fig. 6.) In two of the patients reported on by Rosen et al. [7] the percentage of lipid based on the dry weight of the lung ranged from 16.1 to 21.9, significantly higher than the expected value of 3.4 per cent. A further characteristic of the material, not previously reported, is its affinity for luxol blue, suggesting the presence of phospholipid [11]. Part of the lipid component may be cholesterol, as indicated by its positive reaction to the Schultz method.

The earliest deposits of alveolar proteinosis contain large numbers of sloughed "septal" cells in varying stages of degeneration, consequently the alveolar deposit is not homogeneous and does not stain uniformly. The cytoplasm of some of these cells is P.A.S.-positive, but not strongly so. The walls of the alveoli surrounding recent deposits show increased cellularity and may contain fat-laden macrophages, multinuclear giant cells and lymphocytes, as well as swollen alveolar lining cells. (Fig. 7.) Older proteinaceous deposits have a granular uniform pattern and stain uniformly with the P.A.S. stain. The material fills and distends alveolar spaces and is confluent with adjacent deposits by natural channels through alveolar walls. The alveolar walls may be thin (Figs. 5 and 12), and show no evidence of inflammation, fibrosis or rupture.

Free fat and cholesterol could not be demonstrated histochemically in the doubly refractile crystals present in the acicular spaces. Since multiple minute refractile bodies also were present in the proteinaceous alveolar material, it is

possible that these aggregated to form the larger acicular crystals. It appears that there is an increase in the size and number of these crystals in long-standing cases. They were few in number in Case II in which the disease was symptomatic for approximately five months. In Case I the clinical features extended over a seven-year period, and in sections from the lung bases many of the proteinaceous deposits were replaced by these crystals. (Fig. 8.) The crystals appear to excite a granulomatous reaction in the alveolar walls. Organization of the acicular deposits appears to occur by growth of fibroblasts along the margins of the crystals. As the acicular crystals resolve, there may be fibrous obliteration of the alveoli. In no instances did fibroblasts invade the proteinaceous material.

The characteristic roentgenographic findings of alveolar proteinosis [7] were present in Case II. (Figs. 11A and B.) While in some cases reported by Rosen, Castleman and Liebow [7] the roentgenogram of the chest suggested pulmonary fibrosis, this was not confirmed histologically. In Case I of this report the earliest lesion appeared to be a diffuse fine reticular type of "fibrotic" process (Fig. 1A), and at the height of the disease, five years after onset, it appeared to be a trabecular type of "fibrotic process." (Fig. 1C.) The presence of fibrosis was confirmed at autopsy in this case. Whether the fibrosis was a result of concomitant bacterial infection with necrosis and scarring, or whether it was a part of the evolution of lesions of alveolar proteinosis is not determined. It is likely that both the presence of infection and the acicular crystals excited fibroblastic proliferations.

There is need for further etiologic and epidemiologic study of alveolar proteinosis, and for investigation of the possible role which infection may play as a predisposing or complicating factor in this disease.

SUMMARY

1. Two cases of alveolar proteinosis are presented, with morphologic findings. These showed, in addition to the typical lesions of alveolar proteinosis, unusual complicating infections that were the cause of death. The relationship of frequent infections and the possible role of hematologic disorders associated with the disease is not clear.

2. The presence of phospholipid as an additional constituent of the proteinaceous material

may be indicated by the affinity for luxol blue stain.

3. The proteinaceous material, when present for a number of years, may form large acicular crystals of undetermined nature which appear to excite granulomatous reactions in the surrounding alveolar walls. There is fibroblastic growth along crystal margins and eventual fibrous organization of the involved alveoli.

4. Roentgenographic changes suggesting pulmonary fibrosis were confirmed by histological examination. It is suggested that fibrosis may be part of the evolution of the lesions of alveolar proteinosis, apart from the fibrosis caused by intercurrent infection.

Acknowledgment: I am indebted to Drs. Sloan Wilson and William Larson of the Hematology Service and Dr. Martin Fitzpatrick of the Chest Service, Department of Internal Medicine, University of Kansas Medical Center, for permission to publish these cases.

ADDENDUM

Since the preparation of this article additional case reports of pulmonary alveolar proteinosis were found. These are included for completeness [12-21].

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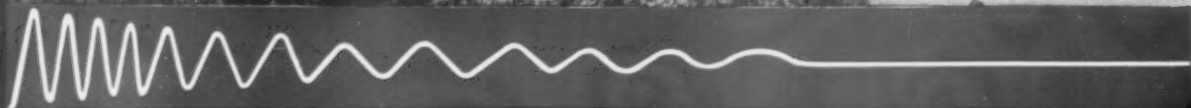
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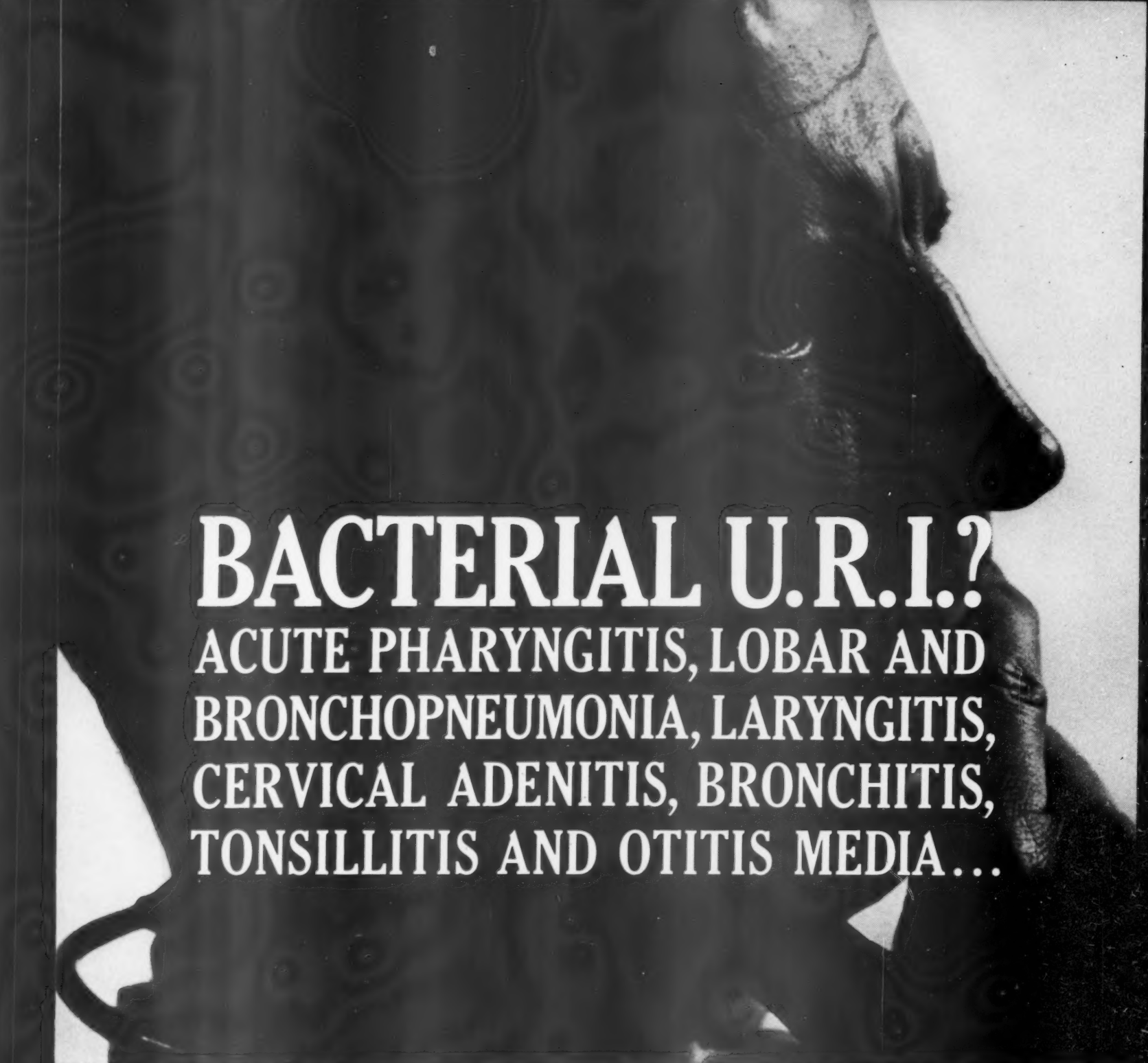
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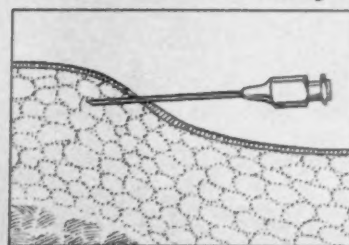
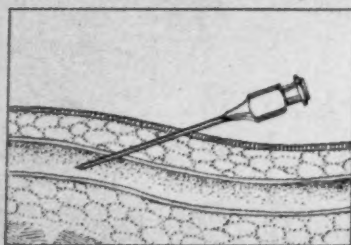
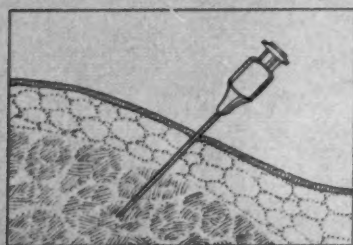
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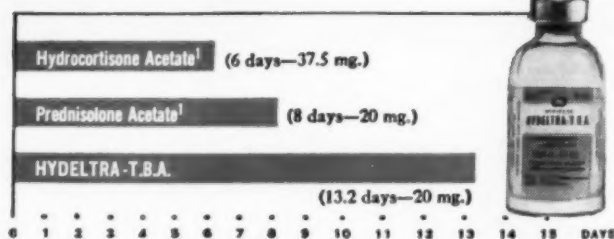
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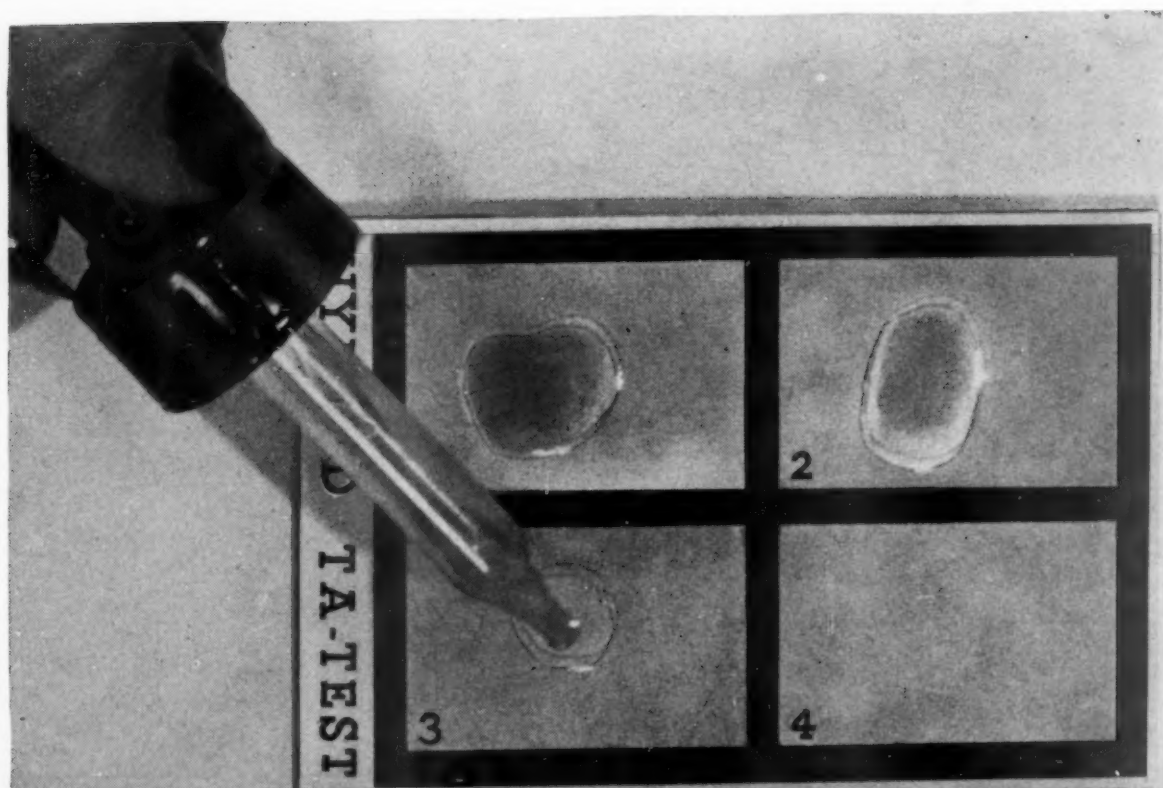
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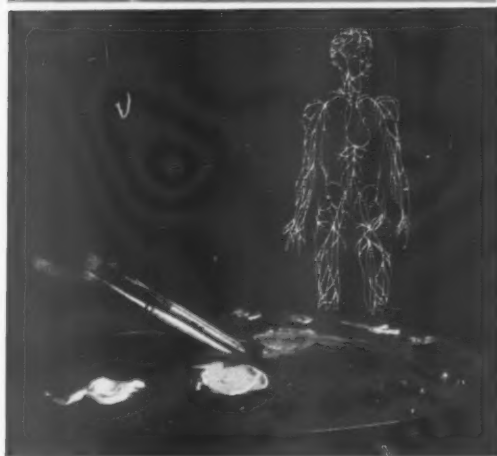
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ADMINISTRATION AND DOSAGE: Adjust dosage to minimum level for optimal therapeutic effect. Recommended initial dose—one 0.5 mg. tablet twice a day for two weeks. Significant side effects are unusual with **MODERIL**, but should they occur, reduce dosage to one 0.25 mg. tablet twice daily. When optimal hypotensive effects are obtained during initial period, this same reduced dosage or less may be used. If greater hypotensive effects than those observed during this period are required, cautiously increase dose by 0.25 mg. per day (up to 2.0 mg. per day) and consider combined therapy. Doses should be taken after meals to minimize possible adverse effects of increased gastric secretion.

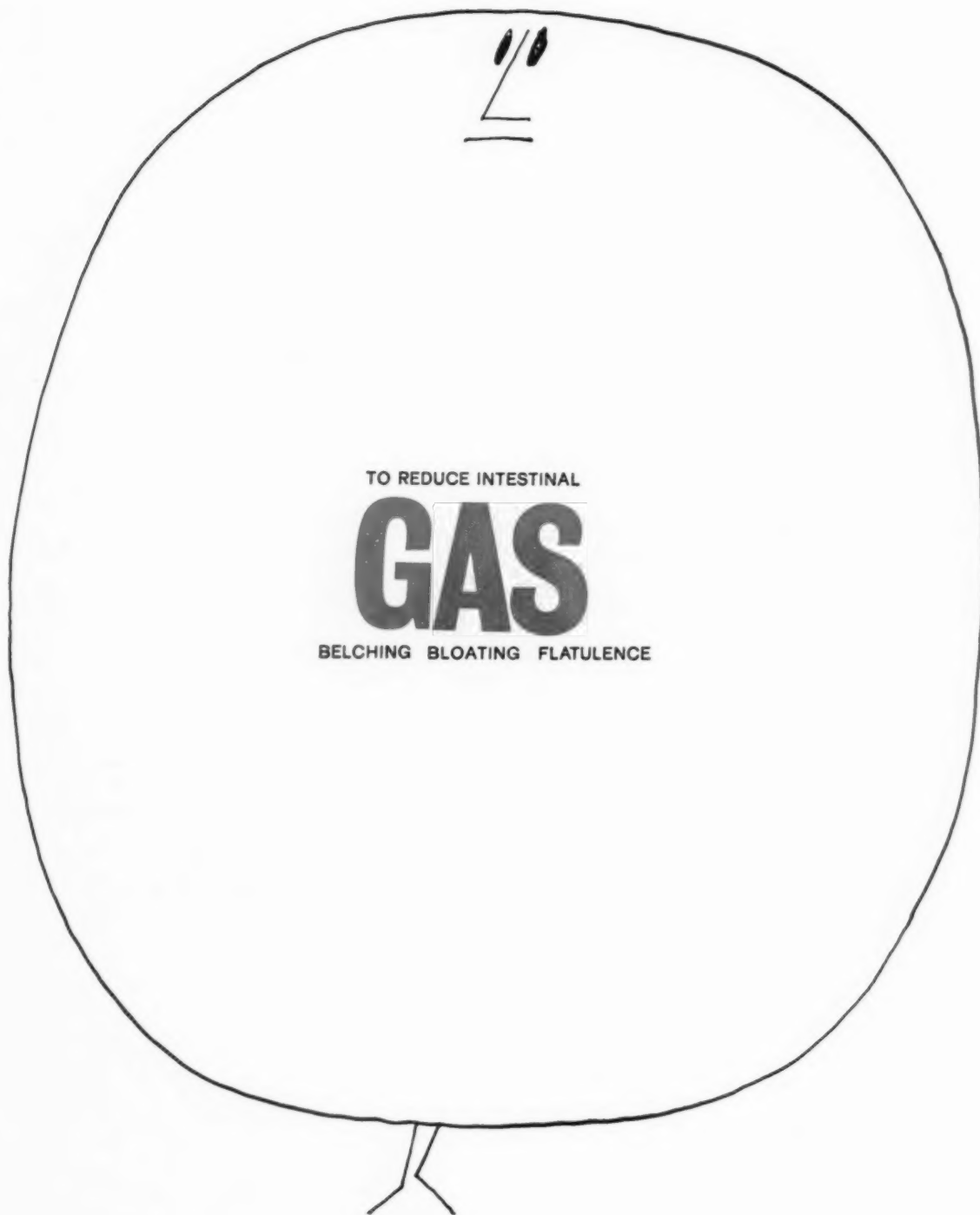
Initial dosage for children 3-12 years of age is up to 0.25 mg. twice daily for one week. Children should be observed closely and when therapeutic effect is achieved, this dose should be reduced by half, i.e., 0.25 mg. daily.

SIDE EFFECTS: Same type as with reserpine but usually with reduced incidence or severity, e.g., mental depression, bradycardia, nightmares, and fatigue. Nasal stuffiness or congestion may occur but usually disappears with discontinuation of the drug or on use of topical vasoconstrictors or antihistamines. Increased frequency of defecation and/or looseness of stools is an occasional reaction. There have been occasional reports of serious hypotension in persons on *Rauwolfia* compounds who undergo surgery with general or spinal anesthesia. It is suggested that **MODERIL** be discontinued two weeks before surgery, when feasible, or other appropriate measures be taken.

PRECAUTIONS: Because rauwolfia preparations may increase gastric secretion, **MODERIL** should be used with caution in patients with a history of peptic ulcer.

SUPPLIED: Yellow, scored, oval tablets of 0.25 mg., bottles of 100 and 500; salmon, scored, oval tablets of 0.5 mg., bottles of 100.

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A biochemical compound
used to diminish intestinal
gas in healthy persons
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Friedman, A. P., and Merritt, H. H.: J.A.M.A. 163:1111 (Mar. 30) 1957.

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Dosage: 1 or 2 tablets every 4 hours, according to need, up to 6 per day.



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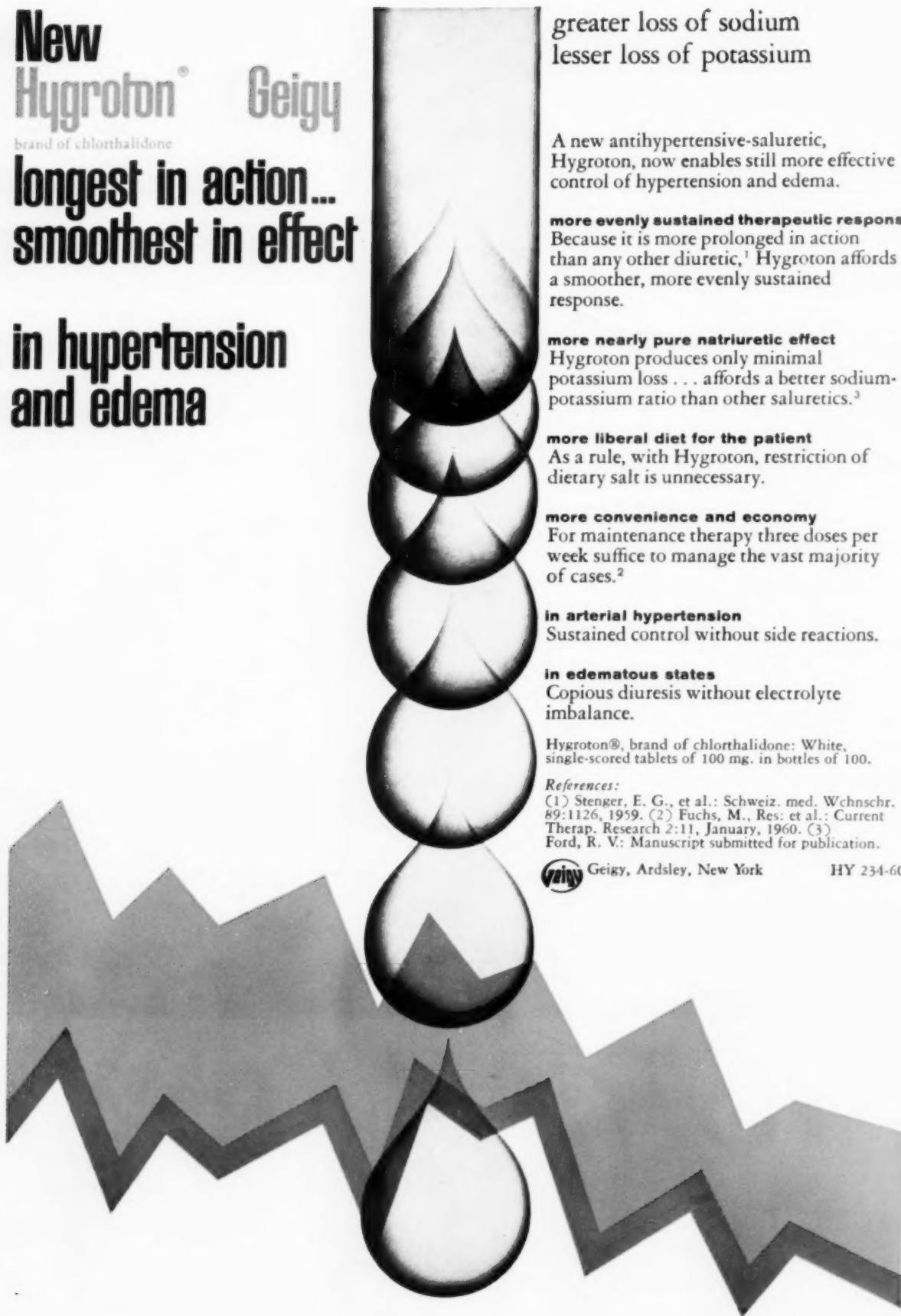
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(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr.
89:1126, 1959. (2) Fuchs, M., Res: et al.: Current
Therap. Research 2:11, January, 1960. (3)
Ford, R. V.: Manuscript submitted for publication.



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1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.

BENEMID is "remarkably free from toxic side reaction....Patients tolerate the drug well."²

2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

"Probenecid BENEMID is the drug of choice as a uricosuric agent. Treatment should be instituted with 0.25 Gm. given twice daily for one week, then increased to 0.5 Gm. twice daily thereafter, without interruption."³

3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

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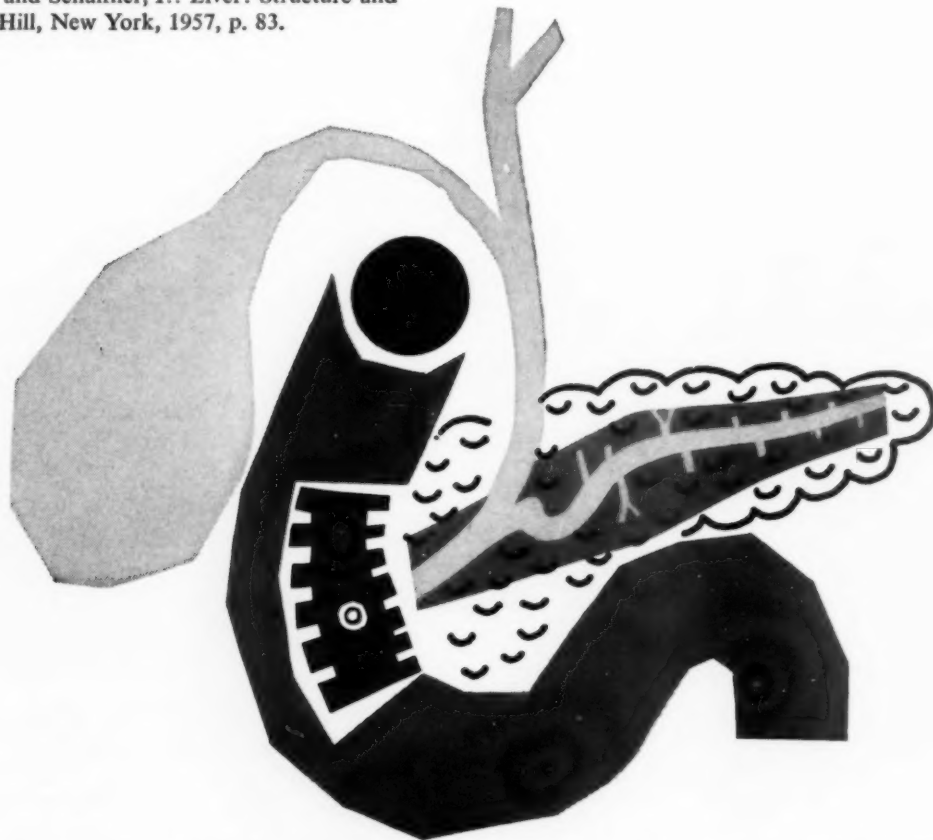
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how does diet affect the production of bile?

High-protein diets produce the greatest bile flow. Fat is a weaker choleric than protein, and carbohydrates are without choleric effect.

Source: Popper, H., and Schaffner, F.: Liver: Structure and Function, McGraw-Hill, New York, 1957, p. 83.



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*Popper, H., and Schaffner, F.: *op. cit.*, p. 84.

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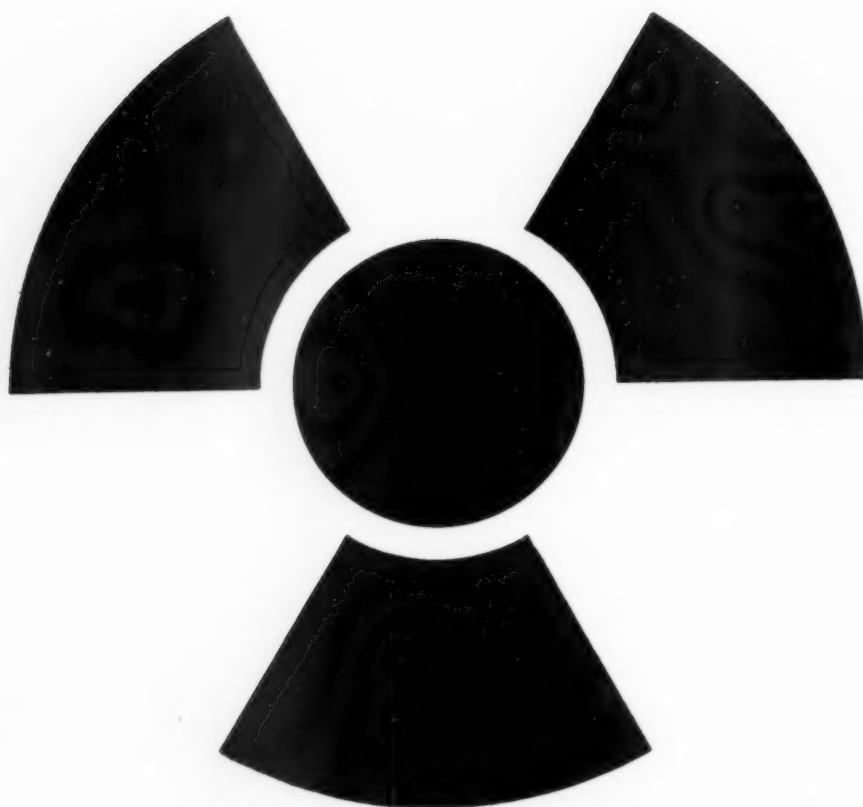
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REFERENCES: 1. H. A. Bickerman in W. Modell, Ed., *Drugs of Choice* 1958-1959, St. Louis, The C. V. Mosby Company, p. 557. 2. L. J. Cass and W. S. Frederik, *New England J. Med.*, 249:132, 1953. 3. L. J. Cass, W. S. Frederik and J. B. Andosca, *Am. J. M. Sc.*, 227:291, 1954. 4. H. Isbell and H. F. Fraser, *J. Pharmacol. & Exper. Therap.*, 107:524, 1953. 5. W. M. Benson, P. L. Stefko and L. O. Randall, *J. Pharmacol. & Exper. Therap.*, 109:189, 1953. 6. *New and Nonofficial Drugs* 1959, Philadelphia, J. B. Lippincott Company, 1959, p. 326. 7. N. Ralph, *Am. J. M. Sc.*, 227:297, 1954. 8. H. A. Bickerman, E. German, B. M. Cohen and S. E. Itkin, *Am. J. M. Sc.*, 234:191, 1957.

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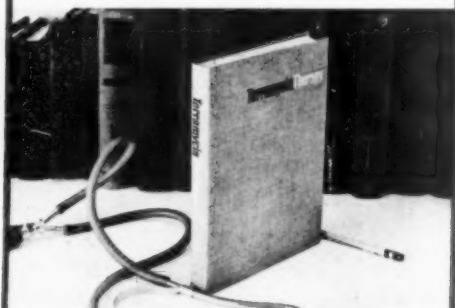
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For intramuscular therapy: Terramycin Intramuscular Solution (200-300 mg. daily) should be adequate for most mild and moderately severe infections. In severe infections, 300-500 mg. daily may be necessary. Dosage for infants and children is proportionately less than for adults.

SIDE EFFECTS AND PRECAUTIONS: Antibiotics may allow overgrowth of nonsusceptible organisms—particularly monilia and resistant staphylococci—thus necessitating close observation of patients. If monilial overgrowth or a resistant staphylococcal infection appears, discontinue medication and institute indicated supportive therapy and treatment with other appropriate antibiotics. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare side effects. There are no known contraindications to glucosamine.

SUPPLIED: Cosa-Terramycin Capsules, 125 mg. and 250 mg. Terramycin is also available in: Cosa-Terrabon® Oral Suspension, a palatable preconstituted liquid containing 125 mg. per 5 cc. teaspoonful, bottles of 2 oz. and 1 pint; Cosa-Terrabon® Pediatric Drops, a palatable preconstituted liquid containing 5 mg. per drop (100 mg. per cc.), bottle of 10 cc. with calibrated plastic dropper; and Terramycin Intramuscular Solution, conveniently preconstituted, 100 mg. and 250 mg. in 2 cc. prescored glass ampules—packages of 5 and 100. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

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Tablets of 10 mg.

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1. Cameron, E.: The Use of Tofrānil in the Aged, *Canad. Psychiat. A. J. Special Supplement*, 4:S160, 1959. 2. Christe, P.: Indications for Tofrānil in Geriatrics, *Schweiz. med. Wchnschr.* 90:586, 1960. 3. Schmied, J., and Ziegler, A.: Tofranil in Geriatrics, *Praxis* 49:472, 1960.

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Hesperidin, *Hesperidin Methyl Chalcone*, or *Lemon Bioflavonoid Complex* are prescribed as therapeutic adjuncts for control of vascular and capillary damage and abnormal cellular metabolism associated with many stress conditions.

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Reports show older people have a high incidence of capillary fragility (6). In a group of 111 patients, capillary weakness was noted to be greatest in the fifth and sixth decades (5).

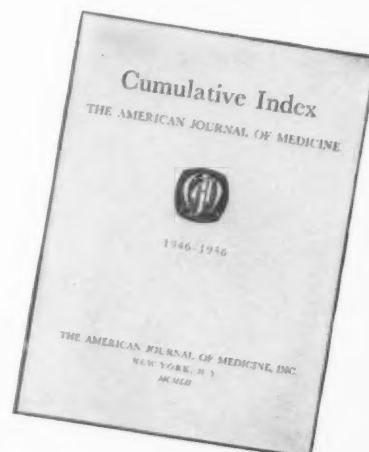
Hypertensives (7, 8, 9) and those with chronic diseases such as arteriosclerosis, diabetes and rheumatoid arthritis, have shown varying degrees of capillary involvement. Hemorrhagic conditions of the brain and heart have shown localized injury in the capillary (10, 11).

Capillary fragility has been shown to be associated with many bacterial, viral and inflammatory diseases (12-23).

Various bioflavonoid materials have been evaluated for their effect upon the capillary. Degree of fragility has been determined by numerous procedures (24-30).

The therapeutic rationale of combining *Hesperidin* or other *citrus bioflavonoids* with ascorbic acid or other therapeutic agents is based on the premise that capillary weakness may be a contributing factor to the disease state and that capillary integrity should be maintained. *Citrus bioflavonoids* in conjunction with ascorbic acid appear to enhance the efficacy of other therapy, and help control such factors as infection, stress and nutritional deficiency even in cases not showing capillary weakness.

NOTE: For bibliography (B-701) write Sunkist Growers, Pharmaceutical Division, 720 E. Sunkist Street, Ontario, California.



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in 8 out of 10
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MER/29 reduces both serum and tissue cholesterol, irrespective of diet.¹
In 463 patients, the mean cholesterol was reduced from 324 mg.% to 253 mg.% — an average decrease of 71 mg.%.¹⁻⁶

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concurrent benefits have been reported in some patients receiving MER/29. These include decreased incidence and severity of attacks, improved ECG patterns, diminished nitroglycerin requirements, and increased sense of well-being.^{1,4,6-8}

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atherosclerosis "...has been shown to afflict about 77% of American males as early as in the 20-to-30 age range."⁹ With MER/29 you have a new, well-tolerated means of lowering cholesterol — which has been considered "...the *sine qua non* of the atheromatous lesion."⁹

compatible with other cardiovascular therapies: MER/29 can be used along with other measures to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include anticoagulants, nitroglycerin, and PETN.

safety data: Patients have now been treated with MER/29 for relatively long and continuous periods. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. However, since long-term MER/29 therapy may be necessary, periodic examinations, including liver-function tests, are desirable. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

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... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both tissue and serum cholesterol

... no demonstrable interference with other vital biochemical processes reported to date

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... toleration and absence of toxicity established by 2 years of clinical investigation

MER/29

(triparanol)

References: 1. Hollander, W., and Chobanian, A. V.: *Boston M. Quart.* 10:37 (June) 1959. 2. Oaks, W., and Lisan, P.: *Fed. Proc.* 18:428 (Mar.) 1959. 3. Oaks, W. W., *et al.*: *A. M. A. Arch. Int. Med.* 104:527 (Oct.) 1959. 4. Lisan, P.: *Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis.* 2:(Suppl.) 618 (May) 1960. 5. Oaks, W. W.: *Ibid.*, p. 612. 6. Hollander, W., *et al.*: *Ibid.*, p. 637. 7. Halperin, M. H.: *Ibid.*, p. 631. 8. Toro, J.: *Ibid.*, p. 544. 9. Morrison, L. M.: *J.A.M.A.* 173:884 (June 25) 1960.



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Balances the mood — no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient — *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation — *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol's smooth, *balanced* action lifts depression as it calms anxiety — both at the same time.

Acts swiftly — the patient often feels better, sleeps better, within a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly — often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely — no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function — frequently reported with other antidepressant drugs.

Bibliography (13 clinical studies, 858 patients): 1. Alexander, L. (35 patients): Chemotherapy of depression — Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. 3. Beerman, H. M. (44 patients): The treatment of depression with meprobamate and benactyzine hydrochloride. Western Med. 1:10, March 1960. 4. Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. 5. Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. 6. Gordon, P. E. (50 patients): Deprol in the treatment of depression. Dis. Nerv. System 21:215, April 1960. 7. Landman, M. E. (50 patients): Clinical trial of a new antidepressive agent. J. M. Soc. New Jersey. In press, 1960. 8. McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slatery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression — New techniques and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. 9. Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. 10. Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. 11. Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. 12. Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. 13. Splitter, S. R. (84 patients): Treatment of the anxious patient in general practice. J. Clin. & Exper. Psychopath. In press, April-June 1960.

Deprol[®]

 WALLACE LABORATORIES / Cranbury, N. J.

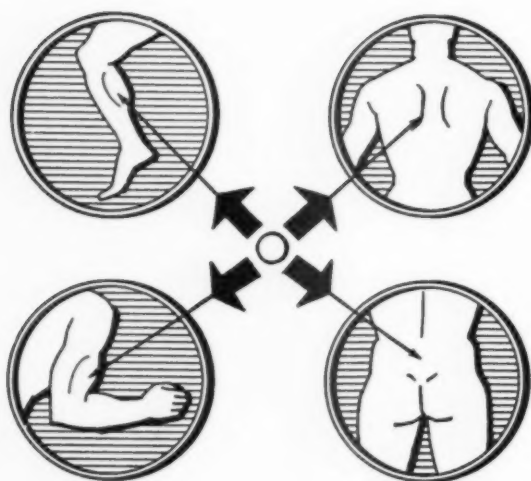
Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

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orphenadrine citrate



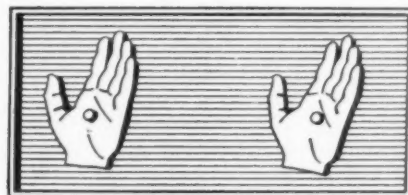
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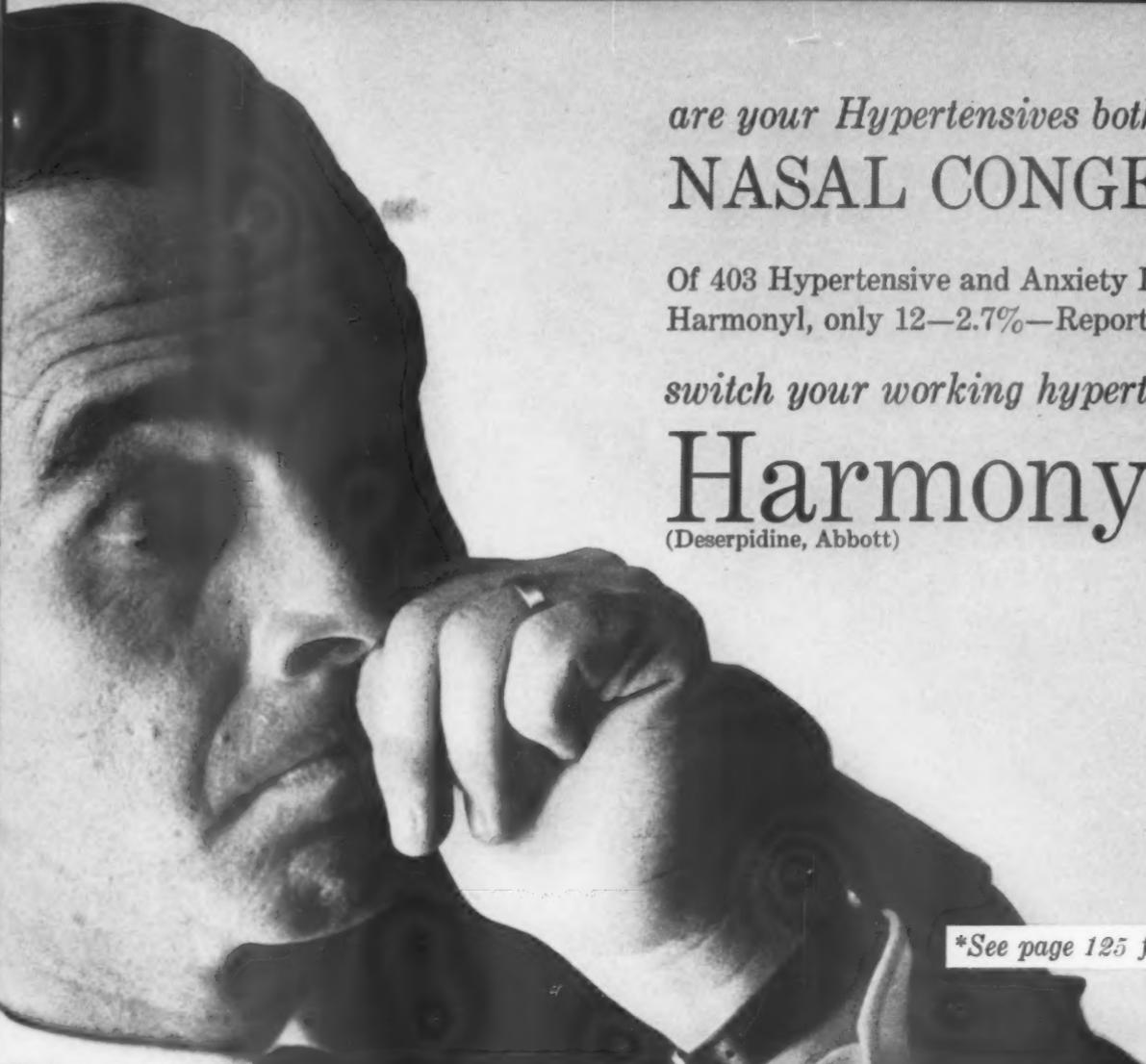
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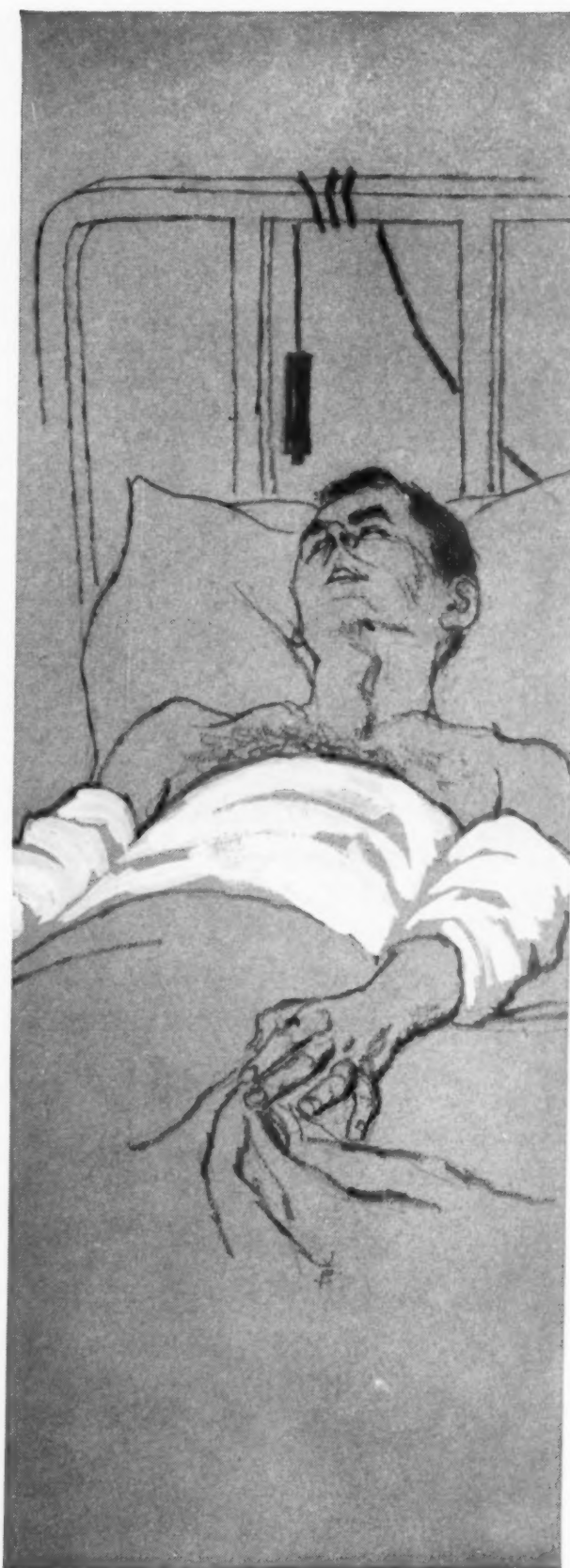
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1. Eisen, H. N., and Tabachnick, M.: Protein Metabolism, M. Clin. North America 39:863 (May) 1955. 2. Jamison, R. M.: General Nutritive Deficiency, Virginia M. Month. 83:67 (Feb.) 1956. 3. Goldfarb, A. F.; Napp, E. E.; Stone, M. L.; Zuckerman, M. B., and Simon, J.: The Anabolic Effects of Norethandrolone, a 19-Nortestosterone Derivative, Obst. & Gynec. 11:454 (April) 1958. 4. Batson, R.: Investigator's Report, Feb. 11, 1956. 5. Weston, R. E.; Isaacs, M. C.; Rosenblum, R.; Gibbons, D. M., and Grossman, J.: Metabolic Effects of an Anabolic Steroid, 17-Alpha-Ethyl-17-Hydroxy-Norandrostenone, in Human Subjects, J. Clin. Invest. 35:744 (June) 1956. 6. Brown, C. H.: The Treatment of Acute and Chronic Ulcerative Colitis, Am. Pract. & Digest Treat. 9:405 (March) 1958.

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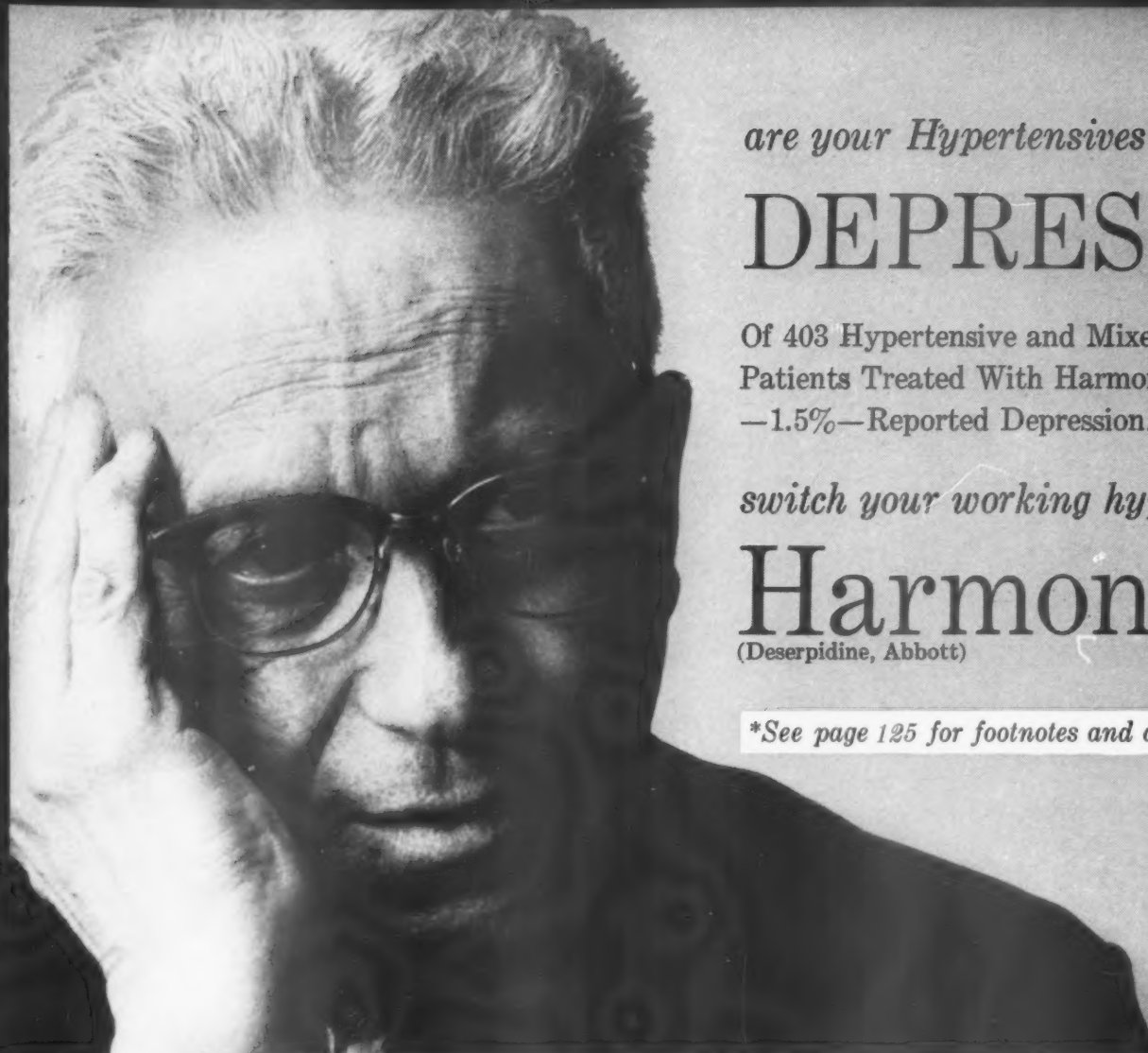
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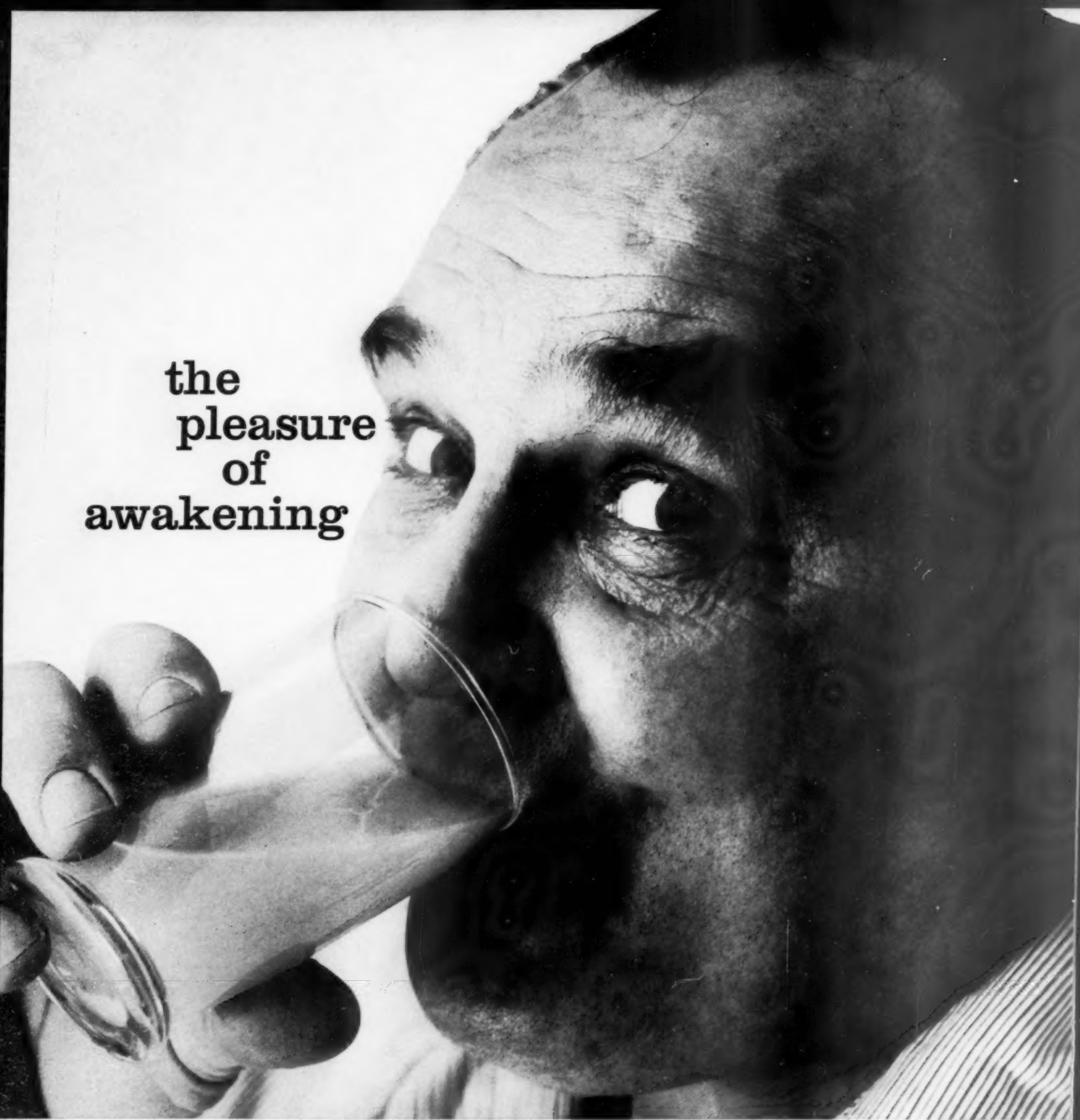
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Lethargy in Drug Treatment of Hypertension

*Of 446 Hypertensive
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Treated With Harmony[®], only 13—
2.9%—Reported Lethargy*

Presented are notes from four clinical studies. Harmony[®] was used as sole agent of therapy by 446 mixed hypertensives, and patients with mild functional/psychiatric disorders. Only thirteen reported lethargy (9 mild) with therapy—an incidence of 2.8%.

Study #1. Two hundred and eighty-three patients treated in private practice, at hospital outpatient clinics, and in office psychiatric practice. Average initial dosage of Harmony[®] was 0.1 mg. to 0.25 mg. three or four times daily. Maximum dose was 6 mg. daily. Nine reports of lethargy (all mild).

Study #2. Eighty patients with benign essential hypertension were studied via "double-blind" method. Mean daily dosage of Harmony[®] was 0.25 mg., with a minimum dosage of 0.1 mg. and a maximum of 0.5 mg. daily. One report of lethargy.


Study #3. Forty patients with hypertension and anxiety neurosis . . . from mild to moderately severe. Half of group had received other antihypertensive agents at one time or another; these were discontinued before and throughout the study. Usual dosage of Harmony[®] was 0.1 mg. three times daily after meals. Sometimes an additional dose was taken at bedtime. Two reports of lethargy.

Study #4. Forty-three patients with tension and anxiety problems typical of general practice. Studied by "double-blind" method. Dosage was 0.25 mg. Harmony[®] three times daily. One report of lethargy.

Generally speaking, these investigators feel Harmony[®] therapy produces the desired results with fewer and less severe side-effects than are sometimes seen with other agents. There is less disruption of the patient's ability to live and work normally, and there is seldom any need to curtail or discontinue Harmony[®] treatment because of side reactions.

1. Billow, B.W. et al, The Use of a New Rauwolfia Derivative, Deserpidine, in Mild Functional Disturbances and Office Psychiatry, N.Y. J. Med., 59:1789, May, 1959.
2. Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, 35:415, April, 1959.
3. Rawls, W.B. and Evans, W.L. Jr., Clinical Experiences with Deserpidine in the Management of Hypertension and Anxiety Neurosis, N.Y. J. Med., 59:1774, May, 1959.
4. Frohman, I.P., Tranquilizers in General Practice and Clinical Evaluation of Deserpidine, An Alkaloid of Rauwolfia Canescens, Med. Ann. District of Columbia, 27:641, December, 1958.

switch your working hypertensives to

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DOE288

safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.¹⁻³ Figure #1 graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.³

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in figure #2, the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,⁴ and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.⁵

In figure #3, the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

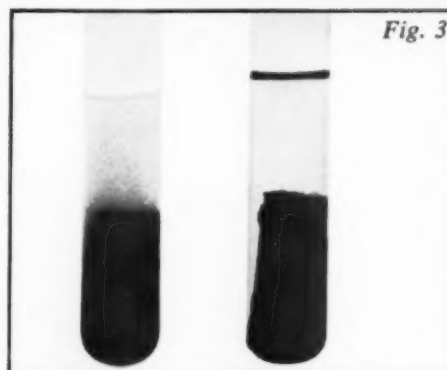
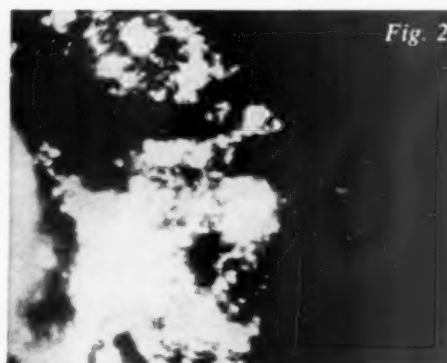
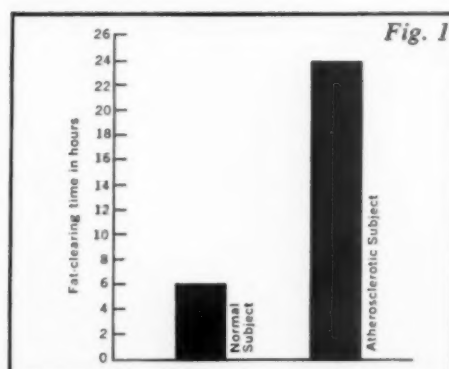
'Clarín', which is heparin in the form of a *sublingual tablet*, has been demonstrated to clear lipemic serum.^{2,6,7} Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarín'.⁸

'Clarín' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

References: 1. Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. 2. Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. 7:225 (Apr.) 1959. 3. Stutman, L. J., and George, M.: Clin. Res. 7:225 (Apr.) 1959. 4. Wilkinson, C. F., Jr.: Annals of Int. Med. 45:674 (Oct.) 1956. 5. Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. 163:727 (March 2) 1957. 6. Fuller, H. L.: Angiology 9:311 (Oct.) 1958. 7. Shaftel, H. E., and Selman, D.: Angiology 10:131 (June) 1959. 8. Fuller, H. L.: Circulation 20:699 (Oct.) 1959.

Clarín*

(sublingual heparin potassium, Leeming)



Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

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References: 1. Cass, L. J., and Frederik, W. S.: *Am. Pract. & Digest Treat.* 2:844, 1951. 2. Blanchard, K., and Ford, R. A.: *Journal-Lancet* 74:443, 1954. 3. Hayes, E. W., and Jacobs, L. S.: *Dis. Chest* 30:441, 1956. 4. Blanchard, K., and Ford, R. A.: *Rocky Mountain M. J.*, Vol. 52, No. 3, 1955. 5. Boyd, E. M., and Pearson: *Am. J. M. Sc.* 211:602, 1946. **A. H. ROBINS COMPANY, INC., RICHMOND 20, VIRGINIA**

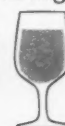
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Prophenpyridamine maleate... 7.5 mg.

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(*exempt narcotic*)

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Each teaspoonful contains:

Parabromdylamine maleate

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1. Schluger, J. et al.: Am. J. Med. Sci. 233:296, 1957.

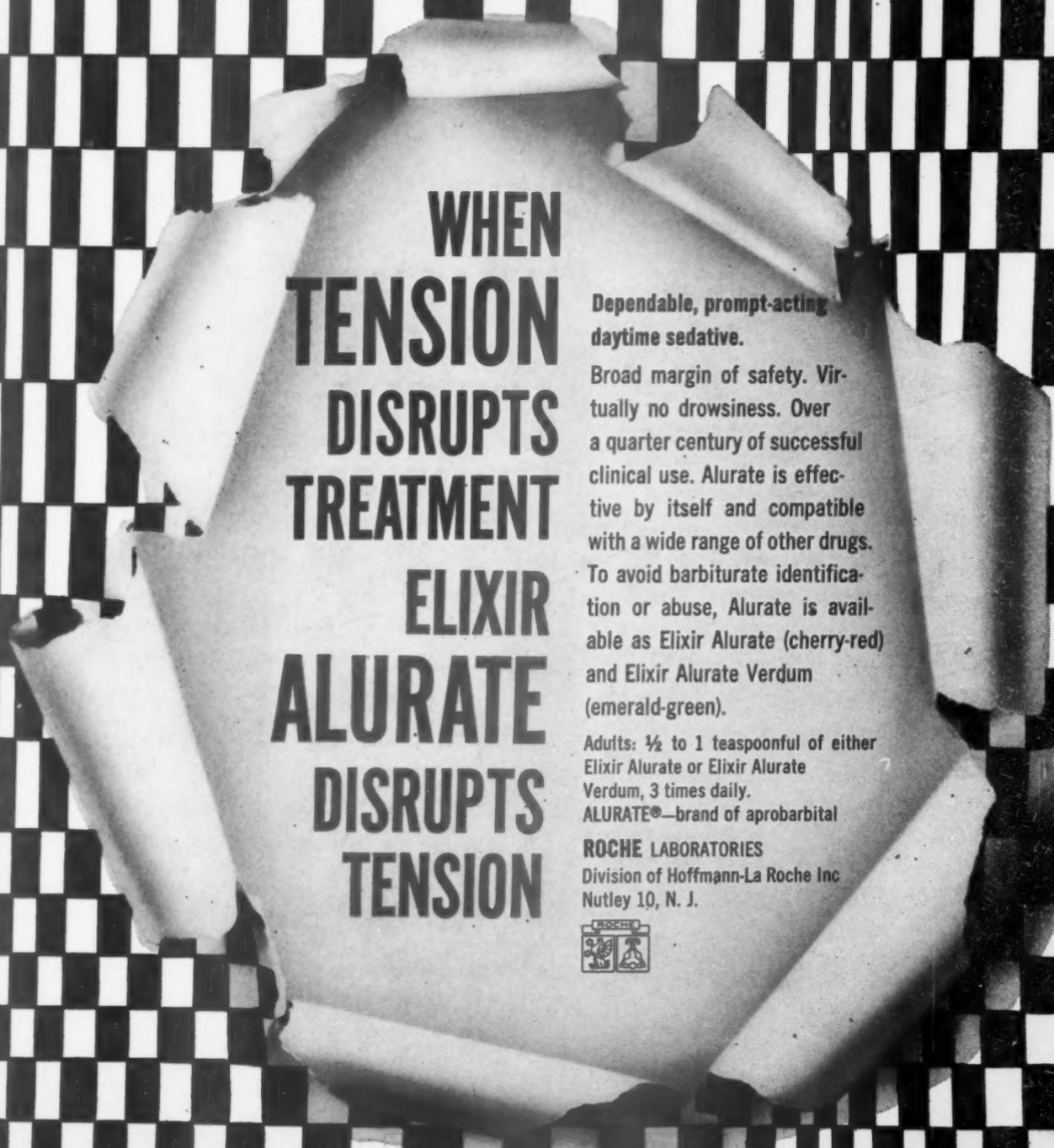
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3. Truitt, E. B. et al.: J. Pharm. Exp. Ther. 100:309, 1950.



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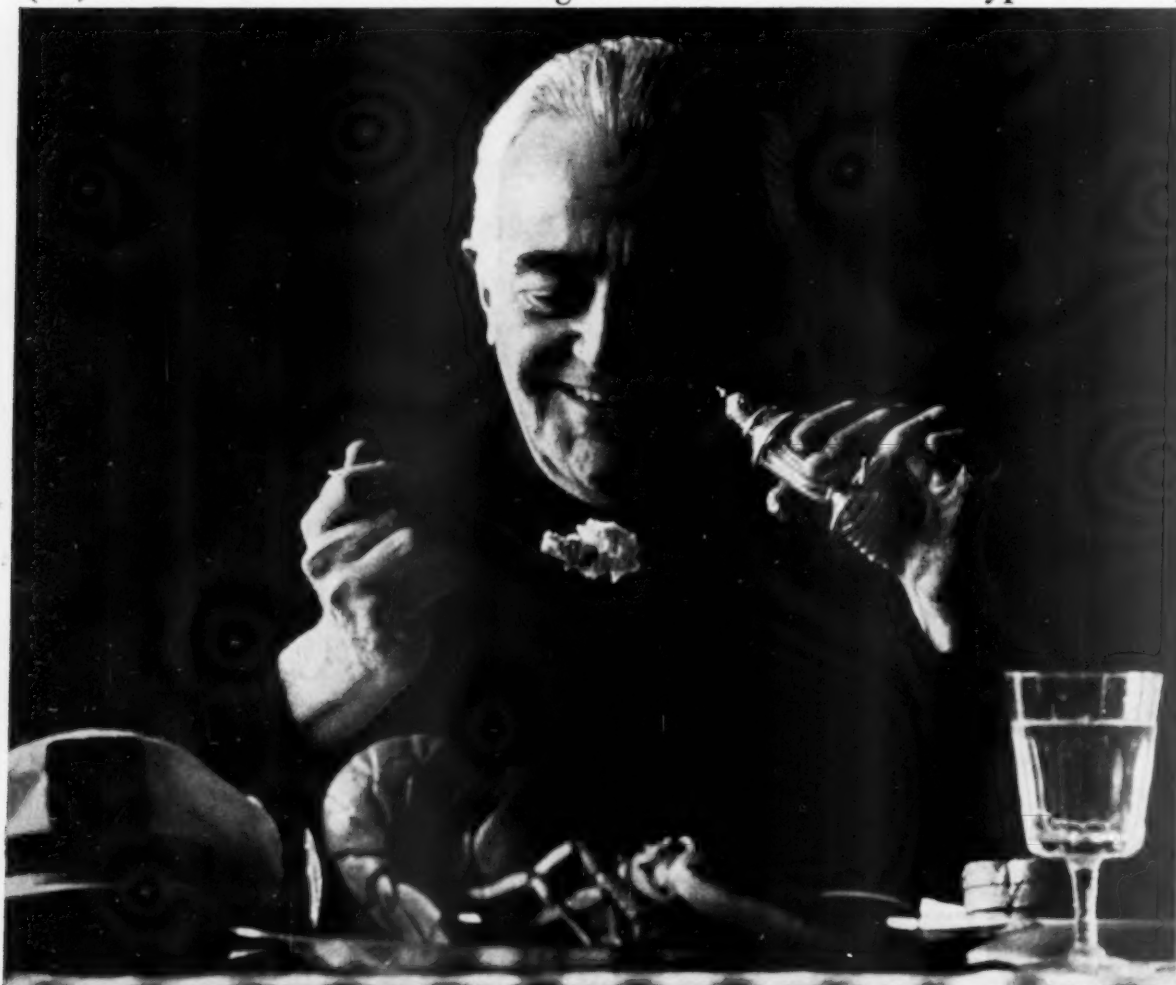
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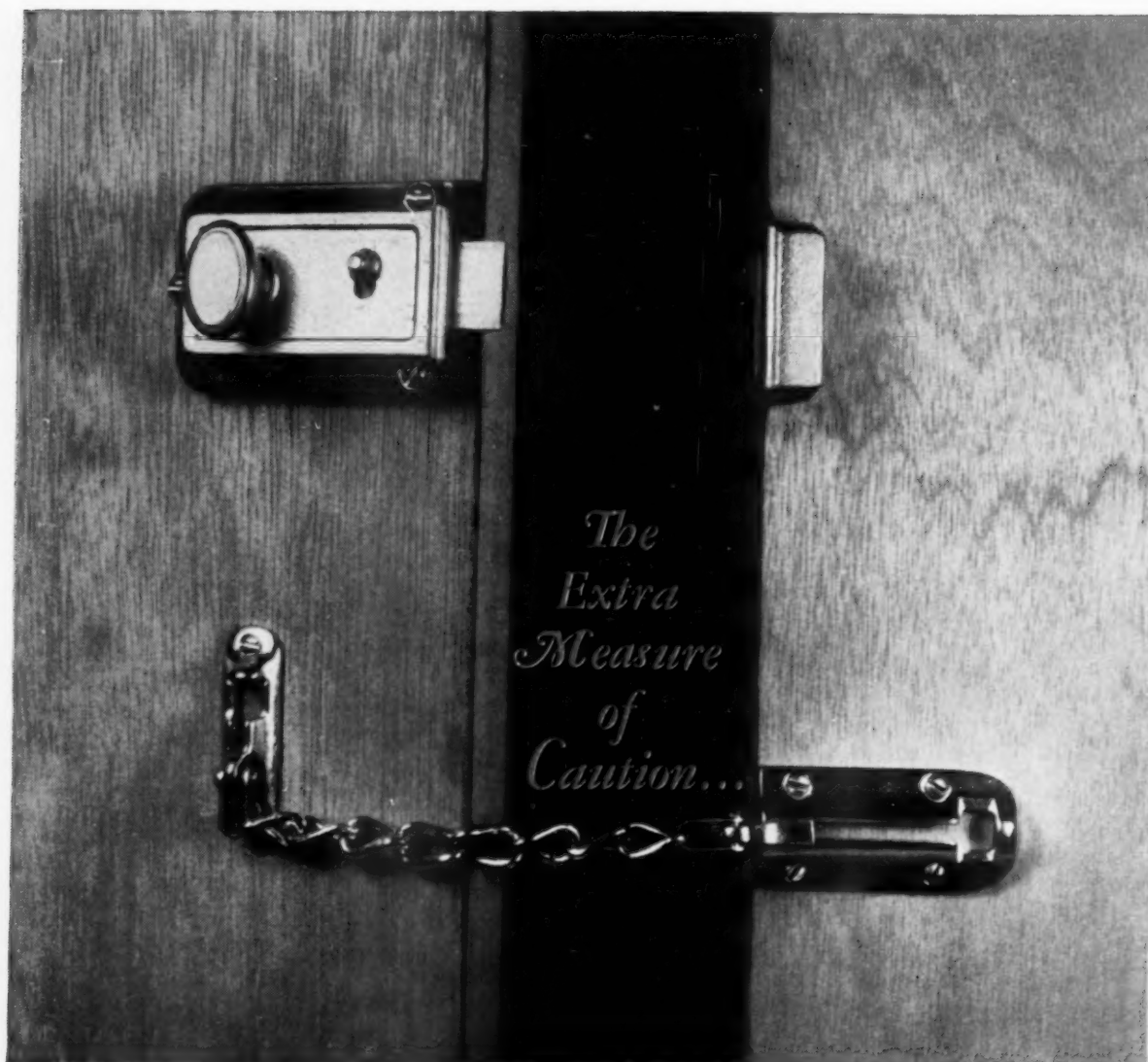
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*From a clinical investigator's report to Merck Sharp & Dohme.

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Dexamethasone

TREATS MORE PATIENTS MORE EFFECTIVELY



MERCK SHARP & DOHME • Division of Merck & Co., Inc., West Point, Pa.

gill



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*** Daricon®**

Oxyphencyclimine hydrochloride

IN BRIEF

DARICON, oxyphencyclimine hydrochloride, is a long-acting highly effective anticholinergic providing potent antispasmodic and antisecretory actions. Each white, scored tablet contains 10 mg. of oxyphencyclimine hydrochloride. DARICON provides 24 hour relief from the pain and discomfort of peptic ulcers, usually with just b.i.d. dosage. A high percentage of refractory ulcer cases have responded well to DARICON.

INDICATIONS: DARICON is valuable for the adjunctive management of peptic ulcers—duodenal, gastric and marginal types; functional bowel syndrome—irritable colon, spastic colon including mucous colitis; pylorospasm, cardiospasm; chronic nonspecific ulcerative colitis; biliary tract disease, including cholecystitis and cholelithiasis; hiatus hernia accompanied by esophagitis or ulcer; gastritis, acute or hypertrophic; duodenitis; bladder spasm with or without cystitis; ureteral spasm, as with stones or pyelonephritis.

SIDE EFFECTS & PRECAUTIONS: Dryness of the mouth is the most common peripheral effect. Blurring of vision, constipation, and urinary hesitancy or retention occur infrequently. These effects may decrease or disappear as therapy continues, or can be minimized by adjustment of dosage. Caution should be exercised when using DARICON in patients with prostatic hypertrophy or glaucoma.

ADMINISTRATION & DOSAGE: The average adult dosage is 10 mg. of DARICON given twice daily—in the morning and at night before retiring. (Dosage should be adjusted in relation to therapeutic response.) As much as 50 mg. daily is acceptable to some adult patients. As little as 5 mg. daily is therapeutically effective in some adult patients.

SUPPLY: DARICON is supplied as a white scored 10 mg. tablet.

More detailed professional information available on request.

PFIZER LABORATORIES
 Division, Chas. Pfizer & Co., Inc.
 Brooklyn 6, N. Y.



It is important, in the over-all management of duodenal ulcers, that the healing process established during the waking hours continue uninterrupted during the sleeping hours.

DARICON provides naturally prolonged antispasmodic-antisecretory protection throughout the night—when ulcer control depends on continuity of anticholinergic activity. A single DARICON tablet usually permits both ulcer and patient to rest undisturbed for 8 to 12 hours. The same prolonged anticholinergic action can be provided during the daytime hours usually with just 1 DARICON tablet at breakfast.



*Science
for the world's
well-being™*



Daricon®
Oxyphenyclimine hydrochloride

another patient with hypertension?





*indicated
in all degrees
of hypertension*

*effective
by itself in most
hypertensives*

HYDROPRES*

HYDRODIURIL® with RESERPINE
(HYDROCHLOROTHAZIDE)

HYDROPRES can be used:

- ▶ *alone* (In most patients, HYDROPRES is the only antihypertensive medication needed.)
- ▶ *as basic therapy, adding other drugs if necessary* (Should other anti-hypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)
- ▶ *as replacement therapy, in patients now treated with other drugs* (In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater anti-hypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

HYDROPRES-25

25 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50

50 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.



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HYDROPRES AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.

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mineral-vitamin-hormone supplement

KAPSEALS®

ELDEC Kapseals help offset the disorders of advancing age for the patient now in his middle years. Supplying numerous valuable dietary and metabolic factors, ELDEC Kapseals provide the patient with comprehensive physiologic supplementation to meet the threat of nutritional and hormonal deficiencies...aid him in meeting the problem of declining health during the years ahead. With ELDEC Kapseals, the patient can plan ahead for tomorrow with a greater assurance of good health and well-being.



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the years of maturity
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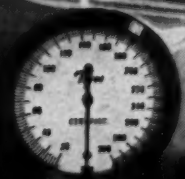
Packaging: ELDEC kapseals are available in bottles of 100.



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PARKE, DAVIS & COMPANY
Detroit 32, Michigan

20990



limit the
blood pressure
swing



Rautrax-N*

Squibb Standardized Whole Root Rauwolfia Serpentina (Raudixin)
and Benzhydroflumethiazide (*Naturetin) with Potassium Chloride

Rautrax-N lowers high blood pressure gently, gradually...protects against sharp fluctuations in the normal pressure swing. Rautrax-N combines Raudixin, the cornerstone of antihypertensive therapy, with Naturetin, the new, safer diuretic-antihypertensive agent. The complementary action of the components permits a lower dose of each thus reducing the incidence of side effects. The result: Maximum effectiveness, minimal dosage, enhanced safety. Rautrax-N also contains potassium chloride—for added protection against possible potassium depletion during maintenance therapy.

Supply: Rautrax-N—capsule-shaped tablets providing 50 mg. Raudixin, 4 mg. Naturetin, and 400 mg. potassium chloride. Rautrax-N Modified—capsule-shaped tablets providing 50 mg. Raudixin, 2 mg. Naturetin, and 400 mg. potassium chloride. For complete information consult package insert or write Professional Service Dept., Squibb, 745 Fifth Avenue, New York 22, N. Y.

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Priceless Ingredient



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RAUDIXIN,® RAUTRAX,® AND NATURETIN,® ARE SQUIBB TRADEMARKS.

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the
bacteria-prone
cold



inner
protection
with...

Tain

(Triacetyloleandomycin, Triaminic® and Calurin®)

safe antibiosis

Triacetyloleandomycin, equivalent to oleandomycin 125 mg. This is the URI antibiotic, clinically effective against certain antibiotic-resistant organisms.

fast decongestion

Triaminic®, 25 mg., three active components stop running noses. Relief starts in minutes, lasts for hours.

well-tolerated analgesia

Calurin®, calcium acetylsalicylate carbamide equivalent to aspirin 300 mg. This is the freely-soluble calcium aspirin that minimizes local irritation, chemical erosion, gastric damage. High, fast blood levels.

TAIN brings quick, symptomatic relief of the common cold (malaise, headache, muscular cramps, aches and pains) especially when susceptible organisms are likely to cause secondary infection. Usual adult dose is 2 Inlay-Tabs, q.i.d. In bottles of 50. **R** only. Remember, to contain the bacteria-prone cold...**TAIN**.

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a division of The Wander Company

PARAFLEX

Chlorzoxazone*

rapidly relieves both pain and stiffness... facilitates recovery

PARAFLEX provides effective skeletal muscle relaxation for 6 hours with a 1- to 2-tablet dose. It relieves painful muscle spasm and improves function in a wide variety of traumatic, arthritic, and rheumatic disorders. PARAFLEX is especially valuable when used in conjunction with physiotherapy and other rehabilitative procedures. Side effects are rare, almost never require discontinuance of therapy.

Dosage: ADULTS—1 to 2 tablets three or four times a day.

CHILDREN— $\frac{1}{2}$ to 2 tablets three or four times a day, depending on age and weight.

Supplied: Tablets, scored, orange, bottles of 50. Each tablet contains PARAFLEX, 250 mg.

*U.S. Patent No. 2,895,877

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330A60

IN WHIPLASH INJURY



When time is precious

INJECTION

Decadron[®]



PHOSPHATE

DEXAMETHASONE 21-PHOSPHATE

will often increase blood pressure
of patients in SHOCK without
evidence of blood loss...



- THE DIRECT APPROACH — ready for immediate use—
needs no reconstitution
- THE DIRECT APPROACH — dramatic response in minutes
I.M. or I.V.—injection can be
as rapid as desired
- THE DIRECT APPROACH — mg. for mg. the most active
steroid in true solution
- THE DIRECT APPROACH — flows readily even through
a small-bore needle
- THE DIRECT APPROACH — needs no refrigeration—
excellent stability

Injection DECADRON Phosphate is the direct approach in allergic emergencies, acute asthma, overwhelming infections (with antibiotic coverage), transfusion reactions, acute traumatic injuries. Injection DECADRON Phosphate can also be used in acute dermatoses, Addison's disease, adrenal surgery, panhypopituitarism, temporary adrenal suppression, rheumatoid arthritis, soft tissue injection. Note: Do not inject into intervertebral joints. Caution: Steroids should not be given in the presence of tuberculosis, chronic nephritis, acute psychosis, peptic ulcer, or ocular herpes simplex.

DOSAGE AND ADMINISTRATION:

Injection DECADRON Phosphate is ready for immediate use intravenously, intramuscularly, or intra-synovially. Dosage varies from 4 mg. or less to 20 mg. or more, depending on the nature and severity of the condition and route of administration.

SUPPLIED:

Injection DECADRON Phosphate is available in 5 cc. vials, each cc. containing 4 mg. of dexamethasone 21-phosphate as the disodium salt.

Additional information on Injection DECADRON is available at your request. DECADRON is a trademark of Merck & Co., Inc.



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Blood pressure that goes up with stress often comes down with SERPASIL®

(reserpine CIBA)

One reason that many cases of hypertension respond to Serpasil is that many cases are associated with stress. Stress situations produce stimuli which pass through the sympathetic nerves, constricting blood vessels, and increasing heart rate. Hyperactivity of the sympathetic nervous system may elevate blood pressure; if prolonged, this may produce frank hypertension. By blocking the flow of excessive stimuli to the sympathetic nervous system, Serpasil guards against stress-induced vasoconstriction, brings blood pressure down slowly and gently.

In mild to moderate hypertension, Serpasil is basic therapy, effective alone "...in about 70 per cent of cases..."*

In severe hypertension, Serpasil is valuable as a primer. By adjusting the patient to the physiologic setting of lower pressure, it smooths the way for more potent antihypertensives.

In all grades of hypertension, Serpasil may be used as a background agent. By permitting lower dosage of more potent antihypertensives, Serpasil minimizes the incidence and severity of their side effects.

*Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.

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Complete information available on request.

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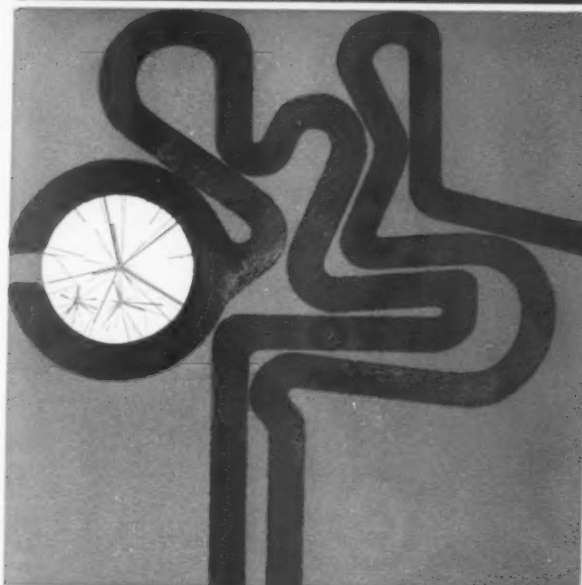


effectively checking gout
retards the disease
by increasing
urate excretion

Anturane^{T.M.}
brand of sulfinpyrazone

(formerly Anturan)

Geigy



In the treatment of chronic gout, Anturane effectively retards further progression by "draining-off" excess urate, thereby preventing new tophus formation.

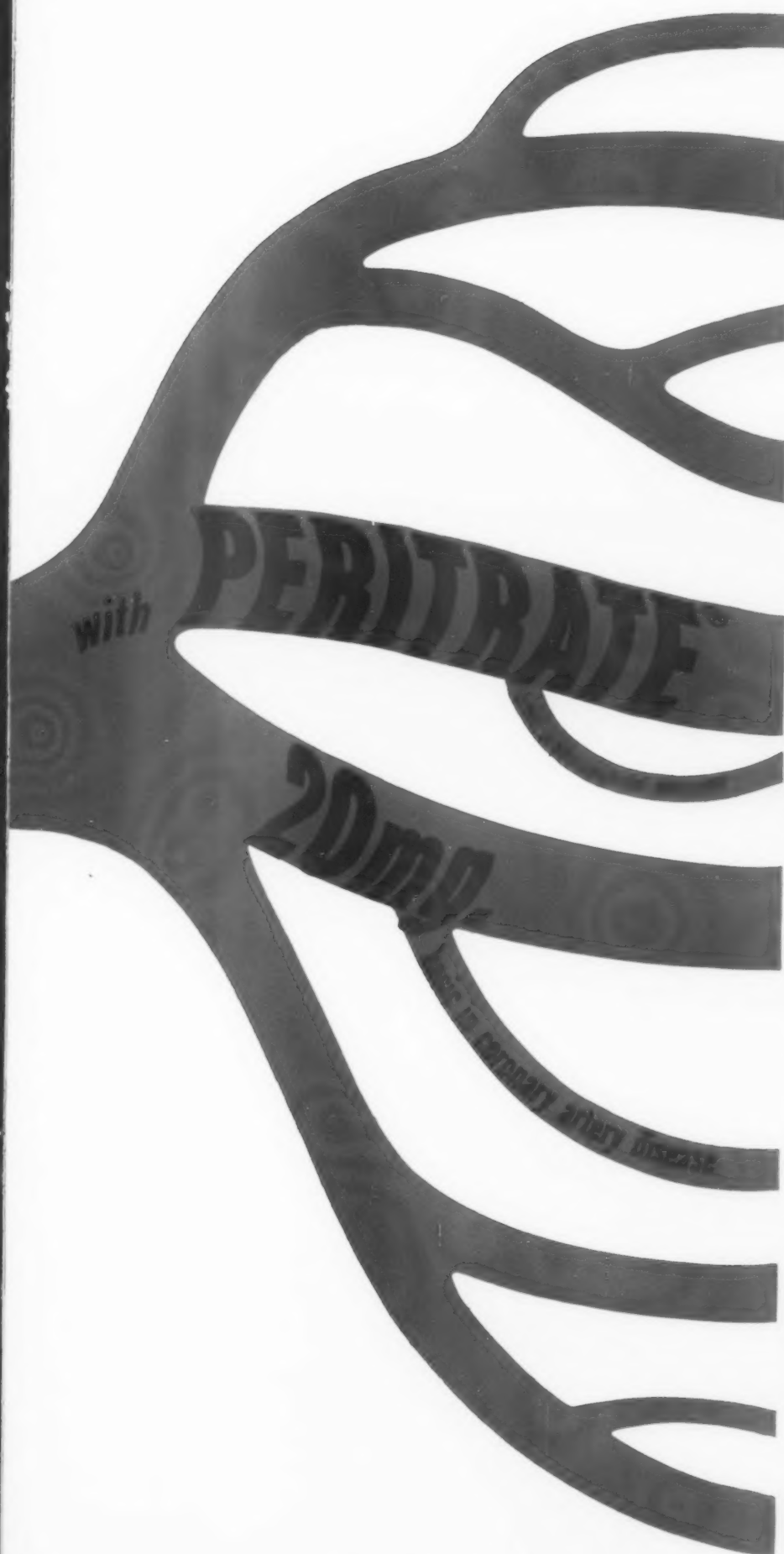
The most potent of all uricosuric agents, Anturane enhances urate excretion by an average of 65 per cent... lowers plasma urate by an average of 30 per cent.¹

The beneficial results are seen in reduced frequency and severity of acute attacks, relief of interval pain, reduction in joint swelling and improved mobility.¹⁻³

(1) Yu, T. F.; Burns, J. J., and Gutman, A. S.: *Ann. & Rheumat.* 7:532, 1958. (2) Kersley, G. D.; Cook, E. R., and Tovey, D. C. Jr.: *Ann. Rheumat. Dis.* 7:326, 1958. (3) Ogryzlo, M. A., and Harrison, J.: *Ann. Rheumat. Dis.* 16:428, 1957.
Anturane, brand of sulfinpyrazone: Scored tablets of 100 mg. in bottles of 100.

Geigy, Ardsley, New York

improve coronary blood flow in angina and postcoronary patients



■ **a proven drug—**

supported by extensive clinical experience during the last ten years

■ **selective physiologic action—**

unlike most nitrites, dilates coronary vessels principally, with minimal peripheral effects, so that coronary blood flow is increased with no significant change in blood pressure or pulse rate

■ **exceptionally safe—**

safe for prolonged use—essentially free from side effects—tolerance has not been reported—no hypotension, orthostatic or otherwise, has occurred—so safe, it is used routinely even after a coronary

■ **effective in mildest to severest angina pectoris—**

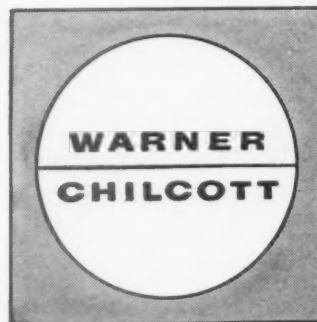
4 out of 5 patients experience reduced frequency and severity of anginal attacks, increased exercise tolerance, lowered nitroglycerin dependence, improved ECG findings

■ **ideal in postcoronary convalescence—**

helps establish and sustain collateral circulation to reduce the extent of myocardial damage, to encourage natural healing and repair, to minimize ensuing anginal attacks

■ **adaptable prophylaxis—**

available in several formulations to meet the individual requirements of patients with coronary artery disease: *Peritrate 20 mg.* for basic prophylaxis, *Peritrate with Pheno-barbital* for the apprehensive patient, *Peritrate Sustained Action* for convenient 24-hour protection with just 2 tablets daily.



MORRIS PLAINS, N.J.



**for every phase of cough...
comprehensive relief**

AMBENYL[®] EXPECTORANT

AMBENYL EXPECTORANT quickly comforts the coughing patient because it is formulated to relieve all phases of cough due to upper respiratory infections or allergies. Combining Ambodryl[®]—potent antihistaminic; Benadryl[®]—the time-tested antihistaminic-antispasmodic; and three well-recognized antitussive agents, AMBENYL EXPECTORANT:

- soothes irritation • quiets the cough reflex
- decongests nasal mucosa • facilitates expectoration • decreases bronchial spasm • and tastes good, too.

Each fluidounce of AMBENYL EXPECTORANT ♦ contains:

Ambodryl [®] hydrochloride	24 mg.
(bromodiphenhydramine hydrochloride, Parke-Davis)	
Benadryl [®] hydrochloride	56 mg.
(diphenhydramine hydrochloride, Parke-Davis)	
Dihydrocodeinone bitartrate	1/6 gr.
Ammonium chloride	8 gr.
Potassium guaiacolsulfonate	8 gr.
Menthol	q.s.
Alcohol	5%

Supplied: Bottles of 16 ounces and 1 gallon.

Dosage: Every three or four hours—adults, 1 to 2 teaspoonfuls; children 1/2 to 1 teaspoonful. 27160

♦ Exempt narcotic

PARKE, DAVIS & COMPANY
Detroit 32, Michigan

PARKE-DAVIS

highly effective,

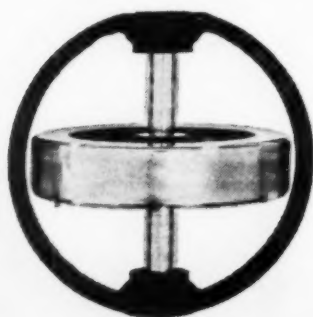
in rheumatoid arthritis...

*still unsurpassed
for total
corticosteroid
benefits*

Aris

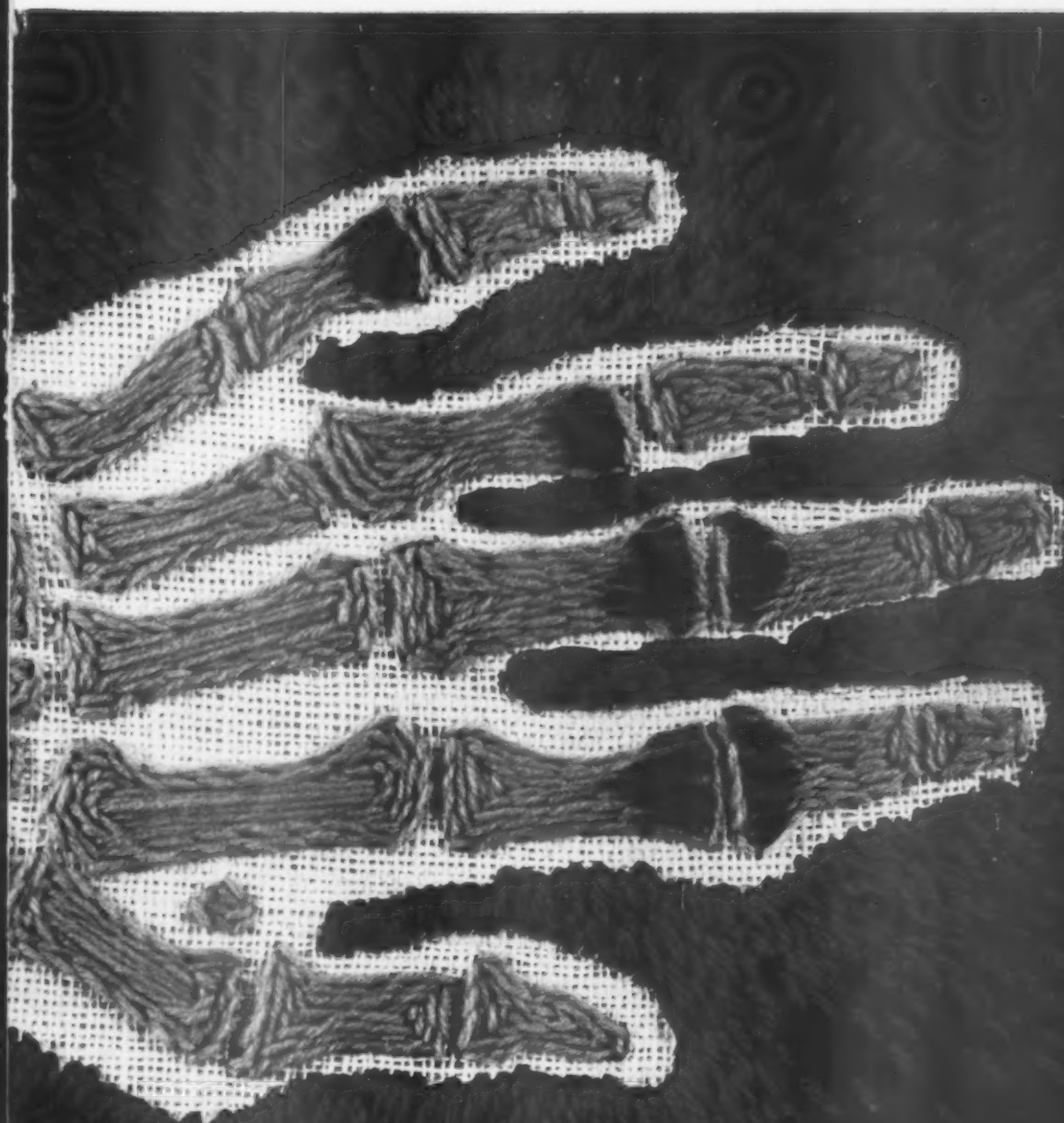
Substantiated by published reports of leading clinicians:

• effective control
of inflammatory
and allergic symptoms⁽¹⁻¹⁰⁾



• biochemical and psychic
balance disturbance
minimal^(1, 3-18)

well-tolerated control



tocort[®]

Triamcinolone LEDERLE

A Promise Fulfilled

All corticosteroids provide symptomatic control in rheumatoid arthritis, bronchial asthma and inflammatory dermatoses. They differ in the frequency and severity of side effects. Introduced in 1958, ARISTOCORT Triamcinolone bore the promise of high efficacy and relative safety.

Physicians today recognize that the promise has been fulfilled . . . as evidenced by the high rate of refilled ARISTOCORT prescriptions.

List of References 1-18 supplied on request.

Precautions: With ARISTOCORT all precautions traditional to corticosteroid therapy should be observed. Dosage should always be carefully adjusted to the smallest amount which will suppress symptoms.

Supplied:

- 1 mg. scored tablets (yellow)
- 2 mg. scored tablets (pink)
- 4 mg. scored tablets (white)
- 16 mg. scored tablets (white)



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.



The physician listens to a tense, nervous patient discuss her emotional problems. To help her, he prescribes Meprospan® (400 mg.), the only continuous-release form of meprobamate.



The patient takes one Meprospan-400 capsule at breakfast. She has been suffering from recurring states of anxiety which have no organic etiology.



She stays calm while on Meprospan, even under the pressure of busy, crowded supermarket shopping. And she is not likely to experience any autonomic side reactions, sleepiness or other discomfort.



She takes another capsule of Meprospan-400 with her evening meal. She has enjoyed sustained tranquilization all day—and has had no between-dose letdowns. Now she can enjoy sustained tranquilization all through the night.



Relaxed, alert, attentive... she is able to listen carefully to P.T.A. proposals. For Meprospan does not affect either her mental or her physical efficiency.



Peacefully asleep... she rests, undisturbed by nervousness or tension. (Meprospan samples and literature available from Wallace Laboratories, Cranbury, N. J.)

Advertisers' Product Index

October, 1960

Abbott Laboratories	
Desbutal*	19, 21, 23, 25, 27
Harmonyl*	119, 121, 123, 125
Norisodrine*	52
Oretic*	132
Selsun*-Iberol*	Insert Facing Page 90
American Sterilizer	
Fluid Therapy	32
Ames Company, Inc.	
Acetest*	4
Decholin*	100
Ayerst Laboratories	
Murel-SA*	68-69
PMB-200*	79
Premarin*	90
Thiosulfil Forte*	Insert Facing Page 36
Burroughs Wellcome & Co., Inc.	
Migral*	36
Ciba Pharmaceutical Products, Inc.	
Serpasil*	148
Serpasil-Apresoline*	Fourth Cover
Singoserp*	30-31, 101
Singoserp-Esidrix*	51
Eaton Laboratories	
Furadantin*	64-65
Tricofuron*	24
Endo Laboratories	
Coumadin*	44-45
Percodan*	97
Geigy Company	
Anturane*	149
Butazolidin*	40
Hygroton*	96
Tofranil*	111
Hyland Laboratories	
TA-Test	88
Knoll Pharmaceutical Company	
Dilaudid*	87
Lederle Laboratories, Div. of American Cyanamid Company	
Aristocort*	154-155
Declomycin*	28-29
Declostatin*	73
Gevrestin*	39, 58
Pathibamate*	16-17
Leeming, Thos., & Company, Inc.	
Clarín*	126
Lilly, Eli, and Company	
V-Cillin K*	76
Maltbie Laboratories	
Dornwal*	66
Massengill, The S. E., Company	
Obedrin*	Insert Facing Page 70
McNeil Laboratories, Inc.	
Paraflex*	145
Parafon*	22
Tylenol*	85
Mead Johnson & Company	
Metrecal Liquid	56-57
Merck Sharp & Dohme, Div. Merck & Co., Inc.	
Aqua Mephyton*	82-83
Benemid*	98-99
Colbenemid*	10-11
Cremomycin*	107
Decadron*	135
Diuril*	48-49
Hydeltra*	86
Hydro Diuril*	62-63
Hydropres*	138-139
Injection Decadron*	146-147
Merrell, Wm. S., Company	
Mer/29*	114-115
Organon, Inc.	
Durabolin*	8
Parke, Davis & Company	
Ambenyl*	152-153
Chloromycetin*	46-47
Eldec*	140-141
Myadec*	12
Pfizer Laboratories, Div., Chas. Pfizer & Co.	
Cosa Terramycin*	Insert Facing Page 108
Daricon*	136-137
Diabinese*	33
Moderil*	93
Vistaril*	54-55
Reed & Carnrick	
Modutrol*	41

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Riker Laboratories, Inc.

Disipal*	34
Lipo-Hepin	13
Medihaler EPI-ISO*	<i>Third Cover</i>
Medihaler-Ergotamine*	20
Norflex*	118

Robins, A. H., Company, Inc.

Allbee*	<i>Insert Facing Page</i> 126
Ambar*	104
Robaxial*	26
Robitussin*—Dimetane*	129

Roch Laboratories, Div. Hoffmann-La Roche, Inc.

Alurate*	131
Librium*	84
Madribon*	14-15
Noludar*	124
Romilar*	106
Tigan*	102-103

Roerig, J. B., & Co.

Enarax*	80
---------	----

Sandoz Pharmaceutical, Div. Sandoz, Inc.

Fiorinal*	95
Mellaril*	74-75

Schering Corporation

Alpen*	81
Fulvicin*	53
Polaramine*	105

Searle, G. D., & Co.

Nilevar*	120
Probitol	77

Sherman Laboratories

Elixophyllin*	130
---------------	-----

Smith-Dorsey, A Division of The Wander Company

Kanulase*	94
Tain	18, 144

Squibb & Sons, E. R., Div. Mathieson Chemical Corp.

Kenalog*	2
Kenalog Parenteral*	59
Mysteclin-F*	134
Naturetin*	108
Raudixin*	78
Rautmax-N*	142-143

Sunkist Growers

Citrus Bioflavonoids	112-113
----------------------	---------

Upjohn, The, Company

Medaprin*	89
Medrol*	35
Orinase*	67
Panalba KM*	159

Wallace Laboratories

Deprol*	116-117
Meprospan*	156
Milpath*	133
Miltown*	42-43
Miltrate*	160
Soma*	60-61

Warner-Chilcott Laboratories

Peritrate*	150-151
Proloid*	1

Winthrop Laboratories

Demerol*	6
Hypaque*	70

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Effective against more than 30 of the commonly encountered pathogens, including **staph** and **strep**, Panalba KM assures you of prompt control in potentially-serious pediatric infections. Panalba KM makes a pleasant-tasting, readily accepted suspension.

When sufficient water is added to fill the bottle to a total volume of 40 cc. (or 60 cc.) and the contents shaken, each 5 cc. (one teaspoonful) contains:

Panmycin (tetracycline) equivalent to tetracycline hydrochloride 125 mg.
Albamycin (as novobiocin calcium) 62.5 mg.
Potassium Metaphosphate 100 mg.

Supplied: In 40 cc. and 60 cc. bottles.

*TRADEMARK, REG. U. S. PAT. OFF.

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

in potentially-
serious pediatric
infections,
make

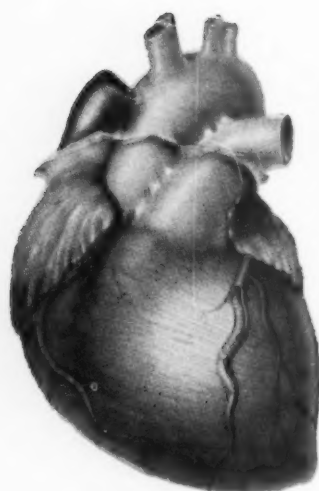
Upjohn

Panalba
KM *Granules

PANMYCIN* PLUS ALBAMYCIN*
WITH POTASSIUM METAPHOSPHATE (KM)

your broad-spectrum
antibiotic
of first resort





**IN ANGINA PECTORIS AND
CORONARY INSUFFICIENCY**

... the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

... it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

Protects your coronary patient better than vasodilation alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important — Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition...and his operative arteries are dilated to enhance myocardial blood supply.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. before meals and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.*: *Circulation* 17:945, May 1958. 2. Friedlander, H. S.: *Am. J. Cardiol.* 1:395, Mar. 1958. 3. Riseman, J. E. F.: *New England J. Med.* 261:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.*: *Circulation* 12:169, Aug. 1955. 5. Russek, H. I.: *Am. J. Cardiol.* 3:547, April 1959. 6. Tortora, A. R.: *Delaware M. J.* 30:298, Oct. 1958. 7. Waldman, S. and Pelner, L.: *Am. Pract. & Digest Treat.* 8:1075, July 1957.

Miltrate®

Miltown® (meprobamate) + PETN



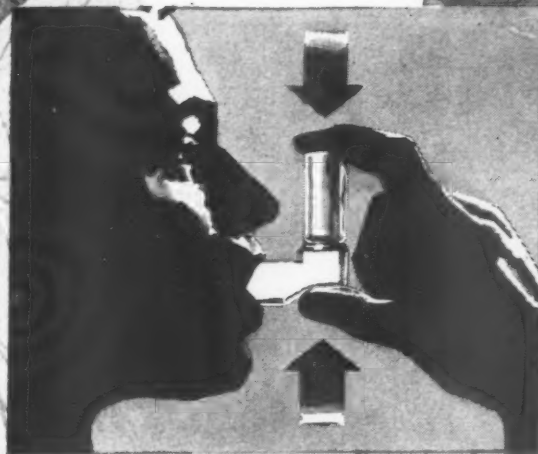
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for immediate asthma relief

and 22½% more vital capacity

Medihaler®

for automatically controlled dosage by aerosol administration



**for maximal convenience
at home or on-the-go**

Available with either of the two
outstanding bronchodilators

Medihaler-EPI®

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each automatically measured dose contains 0.15 mg. epinephrine.

Medihaler-ISO®

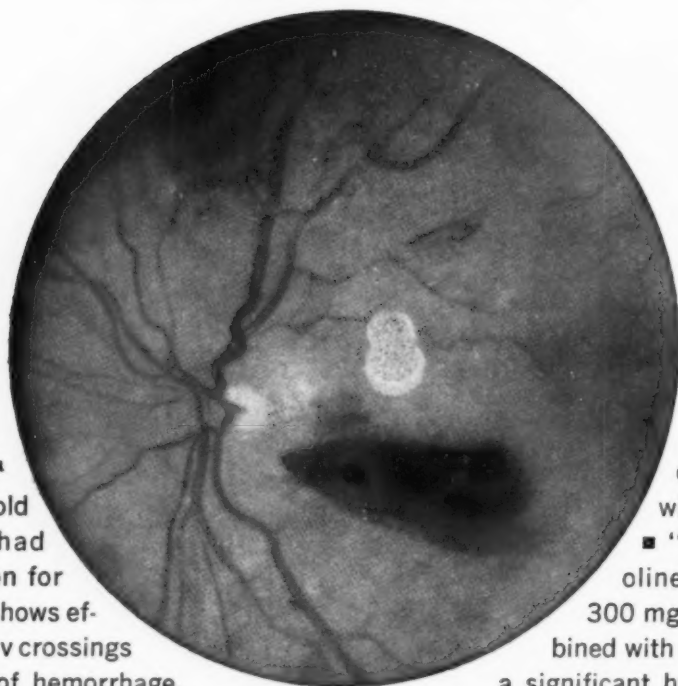
Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each automatically measured dose contains 0.075 mg. isoproterenol.

Optimal effect from Minimal Dosage



Northridge, California

When blood pressure must come down



AS IN THIS CASE:¹

Fundus of 62-year-old female who has had severe hypertension for many years. Photo shows effect of pressure at a-v crossings and various types of hemorrhage.

■ When you see eyeground changes like this—with such hypertensive symptoms as dizziness and headache—your patient is a candidate for Serpasil-Apresoline. With this combination the antihypertensive action of Serpasil complements that of Apresoline to bring blood pressure down to near-normal levels in many cases. Side effects can be reduced to a minimum, since Apresoline is effective in lower

dosage when given with Serpasil.

■ "Hydralazine [Apresoline] in daily doses of 300 mg. or less, when combined with reserpine, produced a significant hypotensive effect in a large majority of our patients with fixed hypertension of over three years' duration."²

Complete information sent on request.

SUPPLIED: Tablets #2 (standard-strength), each containing 0.2 mg. Serpasil and 50 mg. Apresoline hydrochloride. Tablets #1 (half-strength), each containing 0.1 mg. Serpasil and 25 mg. Apresoline hydrochloride.

2/2832 MK

1. Bedell, A. J.: Clin. Symposia 9:135 (Sept.-Oct.) 1957.
2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. 44:456 (March) 1956.

Serpasil-Apresoline[®]

hydrochloride
(reserpine and hydralazine hydrochloride CIBA)

Rx New SER-AP-ES[™] to simplify therapy of complicated hypertension

SER-AP-ES Tablets, each containing 0.1 mg. Serpasil, 25 mg. Apresoline hydrochloride, 15 mg. Esidrix / SERPASIL[®] (reserpine CIBA) / APRESOLINE[®] hydrochloride (hydralazine hydrochloride CIBA) / ESIDRIX[®] (hydrochlorothiazide CIBA)

C I B A
SUMMIT, N. J.